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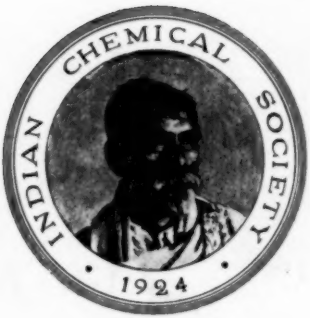

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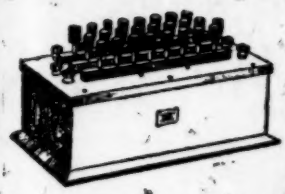

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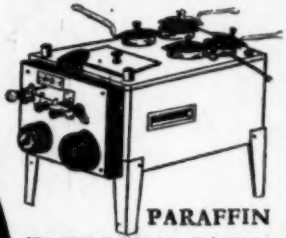

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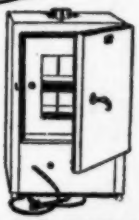

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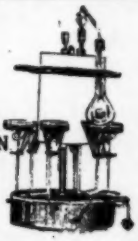

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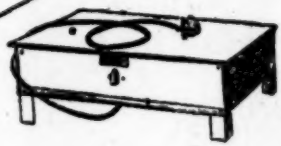

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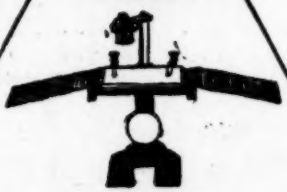

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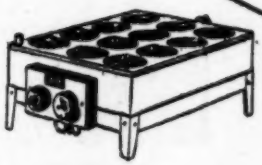

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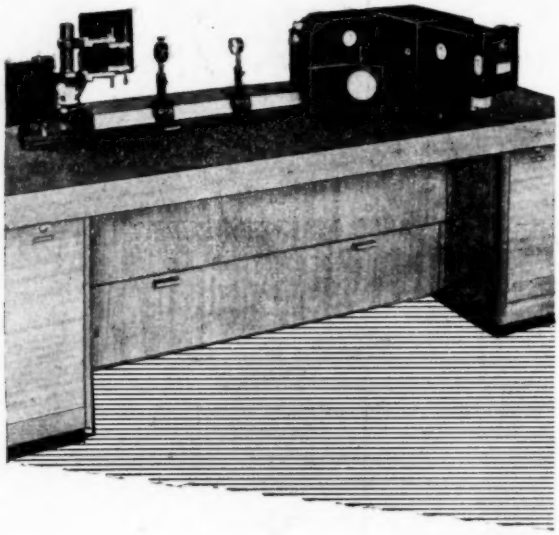

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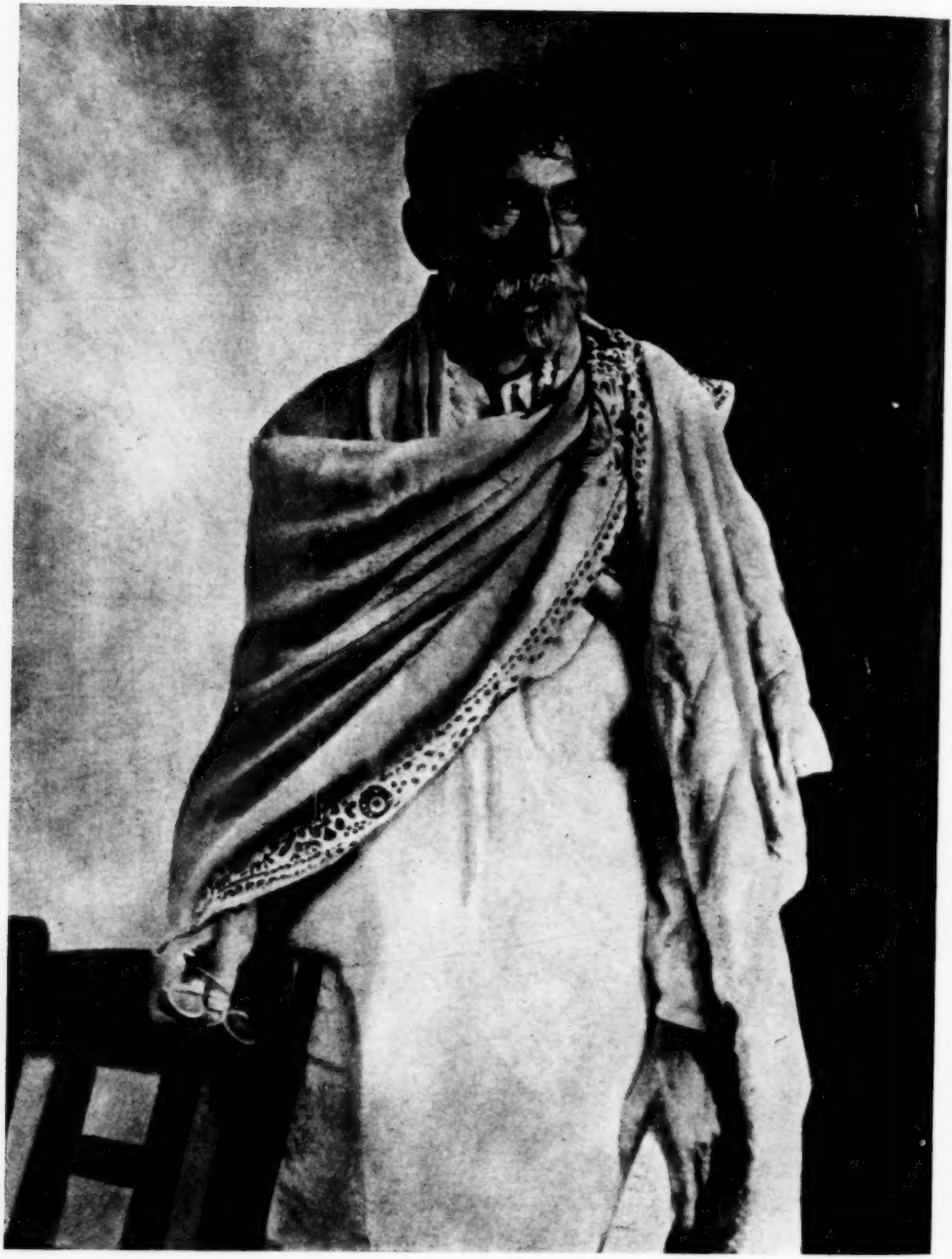


Prafulla Chandra Ray

[Jour. Indian Chem. Soc., Vol. 38, No. 8, 1961]

Acharya Ray and Chemical Research in Modern India

J. N. Ray

Acharya Ray is rightly regarded as the father of chemical research in modern India. But for his tenacity, the advance of chemical education in this country would have been delayed for a long time. In order to judge the real contribution he made in this regard, it is necessary to recall that he was born in 1861, three years after the Indian Mutiny. The state of the country in every direction then was probably at the lowest ebb. The historians have assessed the real significance of the Mutiny in which all kinds of forces, progressive and reactionary, were drawn together. It is now regarded that the failure of the Mutiny was a blessing in disguise. The country woke up to the realisation that the real salvation of India lay in the pursuit of Western Arts and Sciences. It was at this time that Acharya Ray was born. The Calcutta University had been established in 1857 and in his boyhood, education in the country had not been properly organised. When a student in the Metropolitan College, he had to attend the science lectures at the Presidency College, which was the only institution where arrangements for imparting rudimentary education in science existed. It is therefore no wonder that he left for Edinburgh in 1882 before his graduation, availed by the Gilchrist scholarship which was awarded to him in that year. Though he was of literary bent of mind, he realised that the future of this country lay in pursuing science. He came under the tutelage of Professor Crum-Brown who was regarded as a great teacher. In 1885, he obtained the B.A. and in 1888, the D.Sc. degree of the Edinburgh University. His thesis was on Periodic Law. He obtained the Hope Prize and was elected Vice-President of the Edinburgh University Chemical Society. He returned to India in 1888 and secured a junior post at the Presidency College. He accepted this post as it was possible to do some research work; though the equipment was of an elementary nature yet it was far superior to other institutions which had little or no equipment at all.

He published his first work from the Presidency College on 'Conjugated sulphates and isomorphous mixtures of the copper-magnesium group' in 1891. Before this, he was engaged in determining adulteration of foodstuffs—a subject of public interest at that time in Calcutta. The results were published in the Journal of Asiatic Society of Bengal[13].

In 1896, he was able to isolate mercurous nitrite, a real land-mark in his career. It may be recorded that this discovery was made when he was engaged in gas-analysis. In his attempted purification of an impure sample of mercury, the first indication was obtained for the formation of mercurous nitrite. This was obtained as yellow thin crystals when dilute nitric acid containing 13-14% of N_2O_5 reacted with mercury in the cold[5] (J. Asiatic Soc., 1896). The journal of Asiatic Society can scarcely be called a scientific journal, yet this paper was noticed by the Nature. The results were later on published in detail in the Journal of the Chemical Society, London. Subsequently a neat method was devised for the preparation of mercuric hyponitrite[13]. This consisted in reacting mercuric nitrite with potassium cyanide, the latter was oxidised to cyanate, and the nitrite was reduced to hyponitrite. He then began an investigation on the preparation of nitrites of alkaline earths.

These were prepared in a pure state for the first time and it was noticed that magnesium nitrite was the least stable and formed a link between the nitrites of Zn and Cd and those of Ca, Ba and Sr[18,21,24-26]. The double nitrites of Hg (ic) with alkaline earths revealed that the combining power of mercuric nitrite was increased as the atomic weight of the other metal decreased[28]. It was found that the salts had the following compositions:

$$3\,Hg(NO_2)_2.2\,Ba(NO_2)_2,\,5\,H_2O;\; Hg(NO_2)_2.\,Ca(NO_2)_2,\,5\,H_2O;$$
$$Hg(NO_2)_2.4Li(NO_2),\; nH_2O.$$

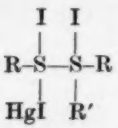
Next we find him interested in the preparation of nitrites of the mercury-alkyl and-aryl ammonium series [31, 32, 35-37, 40-41]. He determined the molar conductivity of mono-amine nitrites and found it to be similar to alkali nitrites. The ethylenediamine nitrites behaved like alkaline earth nitrites. The compounds were represented as

$$(R.NH_2.HgNO_2).NO_2 \quad \text{and} \quad [C_2H_4\,(NH_2)_2.Hg]\,(NO_2)_2.$$

Methylammonium nitrite, alkylammonium nitrites, and tetramethylammonium hyponitrite were investigated between 1911 and 1913. Unlike mercuric nitrite, which forms complex salts with alkyl and aryl amines, the double decomposition of silver nitrite with alkyl amine hydrochlorides gave nitrites of the alkylammonium series. The late Professor B. B. Dey was associated with this work [52-55,57,70]. Professor Dey gave a detailed account of this work in his Acharya Ray memorial lecture[143]. A striking paper was published on the decomposition and sublimation of ammonium nitrite[39] in 1912 in collaboration with Professor N. R. Dhar. Ammonium nitrite was found to vaporise undissociated at 80°. The Nature (Aug. 13th, 1912) in reviewing this work remarked that Professor Ray had added to his success in preparing ammonium nitrite in a tangible form and determining the vapour density of this fugitive compound. This paper was read before the Chemical Society, London. Sir William Ramsay and Dr. Veley paid warm tribute to him for his experimental skill. It was admitted that he and his pupils had greatly increased our knowledge of ammonium and amine nitrites.

With the late Professor J. C. Ghosh, the velocity of decomposition and the dissociation constant of nitrous acid was determined[81]. A solution of nitrous acid can be obtained at 0° by double decomposition and that it can be concentrated by freezing out the water. It was shown that nitrous acid decomposed with a mono-molecular velocity constant. It was recorded that nitrous acid reacted very slowly with urea. Subsequently, Werner utilised this observation when giving his structure of urea.

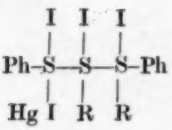
Mercuric nitrite reacts with mercaptans to give mercury mercaptide nitrites of the formula $RSHgNO_2$ and $RSH.\,Hg(NO_2)_2$. These react with alkyl iodides to give sulphonium compounds conforming to the general formula[65-68]



The compound I-Hg-S-S-Hg-I was prepared which exhibited remarkable phototropism.

He tried to differentiate between compounds containing SH grouping which he called 'true mercaptans' and those in which a mercaptanic group arises by tautomerism. These

latter, he called, potential mercaptans[72]. With 2,5-dithic-1,3,4-thiadiazole he got trinuclear condensation product which he formulated as $(C_2N_2S_3)_x.Hg_2O$ (where x=2,3,4 or 6). These furnished, on interaction with alkyl iodide, long-chain sulphur compounds[87]. These compounds are certainly worth re-investigation. It must be remembered that at that time our knowledge of polymers was still to come. The idea of folding chains and cross linkage formation had yet to be advanced. In view of recent advances in knowledge, it is necessary that the long-chain sulphur compounds described by him should receive further investigation. Phenyl mercaptan gave a mercaptide of the formula Ph_2S_3Hg which yielded the sulphonium compound [56] of the formula:



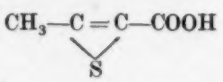
The study of these complex mercaptans led him to investigate the formation and behaviour of some simple sulphides and mercaptans. He found that chloropicrin could be used as a diagonostic reagent for differentiating between real and potential mercaptans. The potential mercaptans always parted with some sulphur in the elementary form when it was allowed to react with this reagent. It was shown that thioacetamide and thiocarbamide behaved like real mercaptans[86]. He showed that a simple reaction like the interaction of ethylene dibromide and alcoholic potassium sulphydrate gave a complex mixture of compounds from which he isolated $HS\text{-}(C_2H_4S)_2\text{-}C_2H_4\text{-}SH$ and the corresponding tetrasulphide $(C_2H_4)_3S_4$ along with the trisulphide [94-95] of the formula $(C_2H_4S)_3$.

Those who were privileged to see him work in the laboratory could not fail to notice his remarkable skill in separating complex mixtures. His experimental skill was comparable to that of W. H. Perkin (Jun.). There may be many views as to the mechanism of formation of these compounds—he did everything he could to establish their constitutions. All the physico-chemical methods known at that time were pressed into service to prove the structures he assigned to these compounds. He studied the permanganate oxidation of trimethylene tetrasulphide[104] which seemed to support the view he held about this compound.

Triethylene trisulphone was obtained by permanganate oxidation and a disulphone with nitric acid. Benzylidenediethylene tetrasulphide and benzylidenediethylene trisulphide were obtained by the interaction of dithioglycol and benzylidene chloride. Diethylene di- and tetrasulphides were obtained as byproducts. Therefore, it is clear that the formation of the several byproducts in the reaction between ethylene dibromide and alcoholic potassium sulphydrate was not due to the presence of polysulphides of potassium present in the alcoholic KSH, which conceivably could have been the case as alcoholic KSH was prepared by the action of H_2S on alcoholic KOH [94-95, 104-106]. A very interesting series of long-chain sulphur compounds of the type $Br\text{-}C_2H_4\text{-}(S\text{-}C_2H_4)_n\text{-}Br$, was obtained by the interaction of ethylene dibromide and dithioglycol[107]. These macro-molecular compounds are certainly worth further investigation by the newer methods of physical-organic chemistry.

Some mercaptans of the purine group were synthesised for the first time[16]. Dr. P. K. Bose[96] was associated with this work. These compounds have acquired new interest as the possibility of their acting as antimetabolites has been suggested recently.

One interesting compound isolated at this time was the compound described as thiocrotonic acid of the constitution[8c]:



This compound was obtained by the action of thioacetamide on chloroacetic acid in acetone solution. Apparently a molecule of ammonia had been lost in the reaction resulting in the formation of a three-membered ring system consisting of two C atoms and a S atom.

Ethyl thioacetoacetate and ethyl thioacetone dicarboxylate were prepared from the related oxygenated compounds with H_2S and HCl. Acid hydrolysis of alkyl derivatives of the above compounds gave mercaptans and alkaline hydrolysis gave mercapto-crotonic acids[138].

Double sulphates of sulphonium bases with sulphates of Cu and Mg groups were described[109] and also those of the phosphonium bases[121].

The true nature of valency had puzzled almost everyone before the twenties of the present century. Acharya Ray started a long series of investigations on the valency of Au, Pt, and Ir. He found that with ethylene dithioglycol, platinic chloride formed complexes of the formula $Pt\text{-}(S\text{-}C_2H_4\text{-}SH)_x$ where $x = 3,4,5,6$ or 8, depending on the experimental condition. Diethyl sulphide reacts with platinic chloride to give (*a*) $PtCl(Et_2S)$, (*b*) $PtCl_2.2\,Et_2S$, (*c*) $PtCl_3.2\,Et_2S$, (*d*) $PtCl_4.2Et_2S$, and (*e*) $PtCl_5.2\,Et_2S.2H_2O$. The compound (*b*) was isolated in six isomeric forms and the constitutions of three of these were settled. One was Blomstrand's *cis* compound, the second was the related *trans* compound, and the third was shown to be $[Pt(Et_2S)_4]\,PtCl_4$. The compound (*c*) was shown to be a molecular mixture of (*b*) and (*d*). This was proved by fractional crystallisation from alcohol. The two constituents were treated with ammonia and their constitutions were confirmed. The compound (*e*) shows a higher co-ordination number than 6. The constitution of these complexes were studied by their action on organic bases and bydetermining their ionisability[122].

With mercaptanic radical, Au also forms compounds in which it can behave as a di-, tri,-tetra-,or a pentavalent atom[163]. An example of bivalent Au is the crystalline compound $2AuCl_2.Et_2S_2$. With ethylene thioglycol, gold chloride gave $2AuCl(C_2H_4S_2)_2$, which was regarded as a compound of Au having an abonormal valency. An example of pentavalent gold was found in the compound $(C_2H_4S_2)_5Au_2$. These claims have been received with indifference, but it may be mentioned that in view of the fact that the compounds of bi-positive and tri-positive silver have now been properly established, it may be worth while to re-investigate these compounds of Ray. Compounds of Ir also received his attention[134,137]. The compound $IrCl_2.3Et_2S$ was isolated in two forms which were *cis* and *trans* isomers. His last contribution was on the subject of fluoro compounds. By double decomposition of anhydrous thallous fluoride with reactive halogen compounds, ethyl and methyl fluoroformate, fluoroacetone, and fluoroacetal etc. were prepared[139-141].

From the foregoing summary of his work it will be seen that though placed under extremely difficult circumstances he was able to carry on researches mainly designed to train pupils who were to spread chemical knowledge in this country. In this he was eminently successful as many of his pupils later on occupied important chairs all over India and established thriving schools of research. The names of the following may be mentioned.

The late Professors J. C. Ghosh, B. B. Dey, H. K. Sen, R. L. Datta, P. Neogi, R. L. Dey P. C. Mitter, A. C. Ganguli and Professors P. B. Sarkar, P. Ray, J. N. Mukherjee, P. C. Guha, J. N. Ray, P. K. Bose, B. C. Guha and several others, who carried his message to the different parts of India. He had the prophetic vision to see that the independence of this country would be attained soon and if we were to reap the benefits of this emancipation, we must have men who would be able to bear the responsibility that would come. It is for this that we regard him as the greatest benefactor to the community. It will be idle to compare his chemical achievement with that of the great savants of the West. He worked with a mission despite all the humiliation he had to suffer and his greatest achievement was the fulfilment of his mission. A story which Mr. Hemendra Prasad Ghosh, the Editor of the Basumati, related at a public meeting may be recorded here. It was in the early part of this century, when Sir J. C. Bose and Sir P. C. Ray were at the Presidency College, the former was insulted by the then Principal of the College. Tagore, the poet, advised Sir J. C. to resign from the college along with P. C. Ray. The National Council of Education (a non-governmental body) would give the scientists facilities for research in a new institution which they would build for them. Bose was all in favour of resigning but Ray advised him not to do so. He was doubtful if another laboratory with necessary equipments could be built easily and it might take ages to build a laboratory. The consequence would be that their researches and training of students would be halted. Therefore, personal insult was considered to be too small a thing in the greater interest of their mission. Had Bose and Ray resigned in 1905, we shudder to think what would have been the state of science in this country now. He was once offered the principalship of a mufiasil college. The acceptance of this post would have removed the stigma of his serving as a Provincial Service officer at the Presidency College, but as that muffasil college did not have adequate laboratory facilities, he promptly turned down the offer. Had he elected to accept this post, there would have been no school of chemistry nor probably the Indian Chemical Society.

The foundation of the College of Science with the munificent donations from T. N. Palit and Rash Behari Ghosh realised a long cherished dream of Acharya Ray. The hopes of the authorities of the University that the Government would supplement the resources of the institution by liberal grants did not, however, materialise. The University got a paltry sum of Rs. 12,000/- a year from the Imperial grant for the upkeep of the laboratories. This again had stilting effect on the growth of research activities. Acharya Ray was educated in Scotland and had acquired the thrifty habits of the Scot. Woe betide the student who dared to waste a drop more of the reagent than was necessary or allowed wastage of tap-water. Every economy was effected so that research work did not suffer. I remember when a very junior student, I was greatly interested in the doings of the seniors who were busy doing research work with the Master. I used to stand hours on end in the corridor to get a glimpse of the Professor and his chosen pupils doing research work in the summer holidays of 1915. One day he caught me at my spying and took me inside and questioned me at length. He then immediately assigned me the task of recovering silver from the various residues which he had kept in several bottles collected over the years. After I recovered and showed him the ingot, he had it weighed and told me the value of the material which I had recovered. I was then asked to convert the Ag into $AgNO_3$ crystals. I remember having prepared quite a few pounds of this material. Next the gold and platinum residues were worked up. From various iodide precipitates, a good amount of iodine was recovered.

He made every student collect in separate bottles all solvent-residues and these had to be recovered. This would give the junior students excellent training and incidentally would reduce the expenses of the laboratory.

Till his last day in the laboratory, he carried on experiments with his own hands. Numerous papers by him without student collaborators would testify to this. His manipulative skill was superb. We used to watch him doing gas analysis fascinated. It was thrilling to watch him transfer minute amount of a gas by the gas pipette.

Much has been said about his teaching methods. He has given an account of his methods of teaching in his autobiography. He believed that "the business of the university was not the transformation of undergraduates into fountains of knowledge. Its business is the difficult task of teaching students how facts are converted into truth. A mind receptive to novelty, capable of wisdom, inclined to moderation—these are the excellences at which it aims. The university has failed when its students are not aroused to passionate discussion amongst themselves or awakened to the study of great books."

Those of us who were privileged to attend his lectures know that he loved to develop a subject historically and gave scant prominence to mere details. His object was to trace the development of human thought. He believed that this approach was the only method to develop the critical faculty in young students. We became intimately acquainted with the past masters like Davy, Faraday, Berzelius, Thomsen, Maxwell, Kekule, Victor Meyer, Ramsay, Rayleigh, and host of other makers of science of the nineteenth century. When we complained about the scanty equipment we had, he would tell us how Berzelius made epoch making discoveries in a small laboratory and his only assistant was the house-maid, Anna. He believed that the personal skill of a man is all that counts, otherwise Berzelius would not have been able to determine the atomic weights with that uncanny accuracy when he had to use an ink-pot as counterpoise. This heartened us a great deal and we took the poor facilities we had as a misfortune of no consequence.

It is well known that he was above everything else a patriot. It occurred to him that the students should know that we had also developed the positive sciences in the past and therefore, we had a responsbilility for developing science at the present time. It was with this object that he embarked on the writing of his monumental History of Hindu Chemistry. Berthelot had written three volumes on "Syriac, Arabic and Middle Age Alchemy". The impression in Europe had gained ground that India's contribution to Chemistry was insignificant. He threw himself heart and soul to the study of Sanskrit sources in the original. The first volume of Hindu Chemistry was published in 1902 and the second volume in 1908. This book received universal encomium abroad and was hailed as a very important contribution to the history of science. This book has been recently revised and enlarged by Professor P. Rây in 1956. The book has been renamed "History of Chemistry in Ancient and Medieval India". Acharya Ray himself wanted to revise his book towards the end of his life but advancing years stood in the way. The Indian Chemical Society has thus fulfilled his wishes in publishing this book. The *Nature* while reviewing this book wrote "Since there is much new material in the book, all those who are fortunate enough to have the earlier edition (P. C. Ray's History of Hindu Chemistry) will wish to have the new one."

With the growth of research activity in India, it became apparent to him that the time has come to publish a journal of our own as it took a long time to have papers published abroad. It was with this object that the Indian Chemical Society was founded in 1924 and he was elected the 'Founder President' of the Society. In reply to the congratulation from the President and Council of the Chemical Society, London, he wrote "The J. C. S. has hitherto been the only organ of chemists throughout the British Empire, and the Publication Committee have been hard put to it to find space for the ever-increasing number of communications and have often been under the necessity of appealing to authors of papers

to abridge them as far as possible. This will explain the necessity of founding the Indian Chemical Society, with an organ of its own.

"More than forty years ago, while a student at Edinburgh, I almost dreamt a dream that, God willing, a time would come when modern India would also be in a position to contribute her quota to the world's stock of scientific knowledge, and it has been my good fortune to see my dream materialise. I have shown in my 'History of Hindu Chemistry' that this branch of science was jealously pursued in ancient India and I have now the satisfaction of finding chairs of chemistry in most of the Universities of India filled by my own pupils, who have also been regular contributors to the J. C. S.——I can scarcely suppress the feelings which arise in me as I am penning these lines."

From the above it will be seen that his whole life was modelled by the one object of rehabilitating this country which had fallen on very evil days at the time of his birth. It did not fall to his lot to see the attainment of 'Independence' but to the future historian of modern India, he will be one of the few, who helped to usher in the 'New Age'. He did not take active part in politics, but he was always in active sympathy with the vanguard of the fight. He used to tell us how Cannizzaro once did shut up his laboratory and shouldered a musket saying 'science can wait but freedom cannot'. He did not shut up his laboratory, but was always there where wanted. His work in connection with the North Bengal floods is a case in point. The correspondent of the Manchester Guardian wrote:

"My enquiries on the spot made it quite clear that Government have lost immensely in prestige over the whole affair and that Non-cooperation has won what government have lost, thanks to the fine work of Sir P. C. Ray's volunteers".

Some Englishmen said at that time if Gandhi had two more associates of the calibre of Ray, Swaraj would have come that very year.

While feverish activities were going on in connection with relief operation, the work in the laboratory[25] continued as usual. This meant extra strain on himself and his students who remained on one duty or another for 14 hours a day. No one grudged putting in this extra amount of work for months on end. Such was his magnetic personality!

Towards the end of his life, when physical handicap stood in the way of his actively working in the laboratory, he used to visit different university-centres where his pupils were engaged in teaching. Dacca, Bangalore, Patna, Allahabad, Madras, Lahore, Bombay, etc. had received frequent visits from him. The students there used to eagerly look forward to these visits. He used to call them affectionately his "grand-pupils". He was in the habit of addressing them and visit them in the laboratory to see them working. Anything new attracted him considerably. I remember once when on a visit to Lahore, he accepted three lecture engagements in an afternoon to my great consternation. He was in very poor health at that time. This touch with the students in various parts of India greatly helped in the spread of chemical knowledge and the torch he kindled thus illuminated the dark corners of many minds in different parts of this sub-continent.

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Currents in Biochemistry

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It is a very striking fact that biochemistry makes wonderful progress in fields in which it has already been very successful, while it makes no progress at all in fields which seem entirely obscure today. If we study these two groups of problems, we will find that the problems in which biochemistry had been, and still is, successful, can all be expressed with symbols of classical chemistry, letters and dashes, while the problems in which we make no progress cannot be expressed in these terms. The reactions belonging to the first group can be repeated in homogeneous solutions, while those of the second involve complicated systems in what looks to be a solid state, linked to structure. To be more specific, biochemistry was most successful in the analysis of intermediary metabolism, in the isolation and the constitution analysis of hormones, vitamins or antibiotics, but remained entirely unsuccessful in the understanding of phenomena like muscle contraction which involves the changes in the physical state of a contractile system. It remained unsuccessful in the analysis of nervous activity which involves electric work in the membranes. The same holds for the establishment of secretions which all involve osmotic work, gradients against concentration. All these latter phenomena not only involve structure but also involve transformation and energy which suggests that our knowledge is deficient in the understanding of the nature of energy.

Physics has given up, a long time ago, asking what things are, and limits itself to asking how things behave. The human mind being built to distinguish things of our own dimension, is entirely unfit to understand the real nature of things, the units of which are very far below the limits of our perception. For this reason physics, limiting itself to the analysis of behaviour, is content with expressing itself in terms of mathematics. The biochemist cannot be satisfied with mathematical formulas because he is dealing with living matter, with particles of one size or another, and his thinking has to be linked to structures, that is, to orientation in space. So,we are led into the problem of the relation of structure and energy. The failure of biochemistry to understand the complex phenomena indicates that our outlook on this relation is wrong. Why it should be so is easy to see. Biochemistry went into bloom at the end of the last century when the atom was an indivisible unit, and the molecule structure built of these atoms. So the biochemical thinking became dominated by the molecular concept which can be represented by the different structural formulas composed of letters and dashes, by which the organic chemists mostly express themselves. However, one feels instinctively that the structure, which forms the foundation of the living machinery, involves the "solid state" and in solid state physics the molecules disappear, more or,less, as units. So, already 20 years ago I made an attempt to apply the ideas of solid states to the living structure hoping to arrive at a better understanding. This attempt, however, remained unsuccessful and did not lead to a better understanding and I can see, today, why. The "solid state" dealt with by the physicists, involves the idea of the very regular repetition of identical units. If these

units are close to one another, the potential barriers may break down and the whole system may fuse into one single unit. The most classical example of such a unit may be copper wire which may be miles long, which conducts electricity, which means that an electron put on one molecule of this unit at one end can be tapped off at the other end within a very short period, indicating that the whole system is, in a way, not an agglomeration of molecules but one single unit, into which these molecules have fused. The reason why this idea was not applicable to biochemistry is easy to see. In biochemistry we do not have the high geometric regularity which we find in crystals, and second, which is equally important, the units are not identical, repetitive. For instance, in the oxidative chain the electrons are known to go from nucleotides to riboflavine, from riboflavine to a cytochrome, from here to another, a third or fourth, and eventually to oxygen. There are also other similar chains which comprise succinic acid, quinones, etc. In any case, the units forming the whole chains are not identical. So, the solid state idea is not applicable to biochemistry and some other means have to be found to understand the intimate relations within a living solid structure in which electrons have a certain mobility, which means that the barriers between the single molecules, and with this the whole molecular concept, break down to some extent. Needless to say, the living material is built of molecules because once we pull the structure into bits we arrive at molecules. But this does not mean that the molecules do not form some sort of supermolecular units, and the rigid molecular concept can be applied to living matter.

Searching for a physical basis for a better approach, I was especially fascinated, during the last years, by "charge transfer". The idea of charge transfer should not be confused with the idea of a transfer of an electron. Any oxidoreduction involves transfer of electrons, but this is not charge transfer. The idea of charge transfer was expressed first by Joseph Weiss in 1942 who found that in certain complexes the one partner of a molecular complex may use the orbitals of the other partner and the donor molecule within this complex may transfer an electron from its ground state to the first empty excited level of the acceptor. This idea was given later a quantum mechanical foundation by the extensive work of Mulliken. The electron may be partly transferred, or be completely transferred, it may need extraneous energy for the transfer, or may go over spontaneously and once it goes over various things may happen to it. The simplest thing which can happen is that the two molecules, the acceptor and the donor, part, interacting with the solvent. The result of this parting will be the production of two free radicals, and free radicals are known to be very reactive. But this is, by no means, the only possibility. The electron transferred on to the acceptor may be transferred from this acceptor to another acceptor. The first acceptor now acts as a donor. From the second acceptor the electron may go to the third, etc. So the electron may go from molecule to molecule once there are certain conditions fulfilled, of which the most important is a very close proximity, which makes the overlap of orbitals possible. Possibly the oxidative chain in biology is, essentially, such a wandering of single electrons from one molecule to another. Since the orbitals overlap, the idea of molecular identity, within this system, becomes very fuzzy and what we actually have in hand is one single electronic system, in which electrons have a more or less free mobility. This leads to a new biochemistry without chemistry, if we understand, by chemistry, changes in which the orbitals and electronic distributions are rearranged. Such a wandering of electrons does not involve covalent changes. The molecules simply form a quantum mechanical framework, on which electrons can move. It seems very likely to me that the living structures are actually such a quantum mechanical framework in which the molecular identity becomes of secondary importance.

I feel very strongly that one is not lost here, entirely, in abstruse speculation. I am

supported in this conviction by a little observation I have made lately. I have found that the carcinogenic substances, that is, the substances which produce cancer, distinguish themselves from other non-carcinogenic substances by the ease by which they give off one electron. This specific quality is evident even in cases in which we compare carcinogenic substances with very closely related homologues which are not carcinogenic and which will be found not to give off electrons under similar conditions. These experiments will be reported in one of the next issues of the Proceedings of the National Academy of Sciences in Washington. In any case, this little experience convinces me that we are not lost here in abstruse speculation but have to do with phenomena which are very closely related, not only to biological processes, but also to everyday problems of medicine.

I actually think that at present there is a new biochemistry being born, built on ideas of wave mechanics. I have, myself, put down my experience in two little books, the one called "Bioenergetics" and the other "Submolecular Biology" in '57 and '60 (Academic Press, New York). Though these little books may be one of the swallows indicating the approach of the new spring, I am, in no way, alone in this new field. An increasing number of research people are engaged in this field. I would mention, in the first place, the Pullmans in Paris who were the first to establish a relation between electronic distribution and carcinogenicity. I would mention B. Commoner of St. Louis who found close relations between photosynthesis, enzymatic activity and related phenomena and electron spin resonance. So, I do think that a new biochemistry is in the process of being born, a biochemistry which relies less on the ideas of classical chemistry than on the ideas of quantum mechanics. I expect that a great forward leap in biochemistry will come when this new line of research will be more generally adopted.

It is a great privilege to offer these few lines to the memory of the Founder-President of the Indian Chemical Society, late Professor P. C. Ray.

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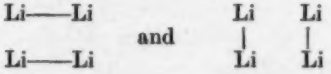
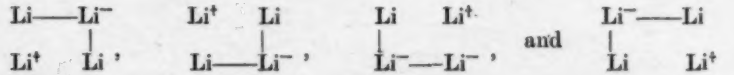
The Nature of the Metallic Orbital and the Structure of Metals*

Linus Pauling

Twenty three years ago it was suggested[1] that for the iron-group transition metals about 8.22 orbitals formed by hybridization of the five 3*d*, one 4*s*, and three 4*p* orbitals are used in the formation of resonating covalent bonds or for occupancy by unshared electron pairs or unpaired atomic electrons. The nature of the remaining 0.78 orbital per atom, called the metallic orbital, was discussed ten years later: it was pointed out[2] that the metallic orbital permits the unsynchronized resonance of covalent bonds from one interatomic position to another by the jump of one electron from an atom to an adjacent atom without the necessity for simultaneous compensatory resonance of other bonds to retain constancy of the electron numbers of the atoms. For example, in lithium metal each atom has one valence electron, permitting the formation of one covalent bond for each pair of atoms. These bonds resonate among alternative positions, mainly those between each atom and its eight nearest neighbors. If each atom were required to remain neutral, by retaining its valence electron, the stabilization in energy through the permitted synchronous bond resonance, corresponding for a square of four atoms to the two structures



would be small. Greater resonance stabilization results from unsynchronized resonance, which permits inclusion of



in the set of resonance structures. The electronic conductance and other characteristic properties of metals may be described in terms of the transfer of positive and negative charges from atom to atom accompanying the resonance of the covalent bonds.

For unsynchronized metallic resonance it is required that each neutral atom and each atom with a positive formal charge have available an unoccupied bond orbital, in order to permit acceptance of another bond. We may confidently assume that significant contributions are made only by structures in which the formal charges of the atoms are -1, 0, or $+1$ only (the principle of electroneutrality[3,4]).

It was pointed out some time ago[5] that a simple statistical calculation leads to the conclusion that for lithium metal resonance of bonds unsynchronized except for the foregoing restriction leads to 43% neutral atoms and 28.5% each Li^+ and Li^-. The experimentally based value 0.72 for the number of metallic orbitals per atom is derived from the properties of the metals chromium to copper, which have metallic valence approxi-

* Contribution No. 2671 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology.

mately 6 and ligancy 12 in the cubic or hexagonal closest-packed structures. The numbers of ways of distributing 5, 6, and 7 bonds among 12 positions about an atom are $12!/5!7!$, $12!/(6!)^2$, and $12!/5!7!$, respectively, which are in the ratios 6:7:6. Hence the corresponding probabilities of occurrence of M^+, M, and M^- in the metal are 6/19, 7/19, and 6/19, which are 31.6, 36.8, and 31.6%, respectively.

For unsynchronized resonance of this sort the atoms M^+ and M, but not M^-, must have a metallic orbital. Hence we conclude that the number of metallic orbitals per atom should be about $0.316+0.368=0.684$. This value closely approximates the value 0.72 found by analysis of the magnetic properties of the metals chromium to copper and their binary alloys.

The difference between the value given by the statistical calculation and that found by experiment is in the direction of a larger fraction of uncharged atoms in the metal than that corresponding to completely unsynchronized resonance of the bonds. This result suggests that the energy required to separate the charges interferes with the motion of the electrons to some extent, so as to increase by a few percent the probability of zero charge.

The above argument permits the discussion of the metallic valence of hyperelectronic atoms to be carried out in a straightforward way. The observed bond lengths in white tin (each tin atom has four ligands at 3.016 Å, bond number 0.52, and two at 3.175 Å, bond number 0.28) correspond[6,7] to the valence 2.64. The expected value is about 2.60, as given by the following calculation. The probabilities 0.30, 0.40, and 0.30 are found for Sn^+, Sn, and Sn^- by the statistical treatment (assuming as a simple approximation 2, 3, or 4 bonds in 6 positions). The atoms have four outer orbitals (hybrids of the 5*s* orbital and the three 5*p* orbitals) and 3, 4, and 5 outer electrons, respectively. Hence Sn^+ can be tervalent (spp) and have its metallic orbital, Sn must be bivalent (s^2pp) to retain its metallic orbital, and Sn^- is tervalent (s^2ppp), with no metallic orbital. The weighted average of the valences is thus 2.60.

The single-bond metallic radius of tin has the value 1.399 Å for a tetrahedral orbital (Sn^+) and 1.434 Å for a *p* orbital (Sn and Sn^-). The appropriate value for white tin is hence 1.424 Å, which leads, with the equation:

$$D(n)=D(1)-0.60\ \text{Å}\ \log n,$$

to the values of bond numbers n quoted in the preceding paragraph.

A similar discussion can be given to other hyperelectronic metals and also bufier metals[8]. For nickel, for example, Ni^+, Ni, and Ni^- are expected to occur in the ratio 0.28: 0.44:0.28. A metallic orbital is required for Ni^+ and Ni, which have, respectively, nine and ten outer electrons to be placed in the eight stable orbitals other than the metallic orbital. This requires that Ni^+ have one unshared pair of electrons; of the other seven electrons, six are involved in bonding and the seventh has an unpaired spin that can contribute to the ferromagnetism of the metal. For Ni, with ten electrons, there are two unshared pairs and six bonding electrons; accordingly Ni contributes nothing to the ferromagnetism of the metal. For Ni^-, with all nine orbitals available for occupancy by electrons, the eleven electrons may be introduced as two electron pairs, six bonding electrons, and one unpaired atomic electron. Accordingly Ni^+ and Ni^- contribute one electron spin to the magnetic moment of the ferromagnetic metal, and, with probability 0.28 for each, the predicted saturation magnetic moment is 0.56 Bohr magnetons, plus the contribution (0.06) of the uncoupled electrons of the conduction band[9]. It is possible that an experimental check on this theory, which assigns the magnetic moment almost entirely to Ni^+ and Ni^-, could be made by a magnetic resonance experiment.

SUMMARY

The properties of the transition metals and alloys indicate that 0.72 orbital per atom is required for metallic character, in addition to the stable orbitals that are occupied by bonding electrons or atomic electrons. Consideration of the electronic structure of metal indicates that an extra orbital of this sort would be needed by the atoms M^+ and M in order to permit unsynchronized resonance of valence bonds, to the extent permitted by the restriction of the electroneutrality principle, but that M^- would not require a metallic orbital. Statistical calculations support the probabilities 0.28, 0.44, and 0.28 for M^+, M, and M^-, respectively. The number of metallic orbitals, the sum of M^+ and M, is thus found to be about 0.72 per atom, in agreement with the value indicated by the magnetic properties of the metals and alloys.

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A Short Review on Alkaloids Occurring in Calabash Curare and Strychnos Barks

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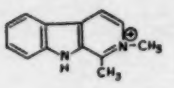
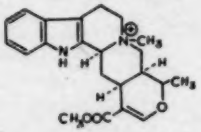
The group of alkaloids which could be isolated from calabash curare and strychnos barks has considerably increased in the last few years. For many of these compounds structural formulas have been proposed. The following tables summarize the available information on the occurrence, empirical formulas, R_c-values, colour reactions, biological activity and (as far as possible) the structure of these alkaloids. The tables contain also the most important references concerning this group of natural products. These tables are an enlargement and a completion of those which had been worked out in the earlier stages of the investigation of these alkaloids[1,2,46].

Alkaloids with known structures from Calabash curare *and* Strychnos *barks*

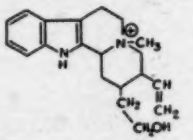
(The references pertain to the papers on structure elucidation).



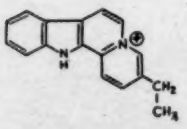
N(b)-Metho-harmin salt
Melinonine F [21]



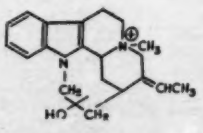
Melinonine A [20]



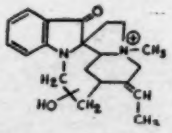
Melinonine B [21]



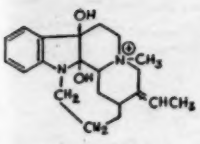
Melinonine G=
Flavopereirine [21,30]



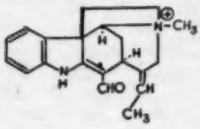
C-Mavacurine [31,32]



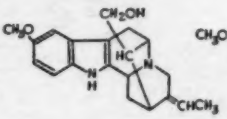
C-Fluorocurine [31,32]



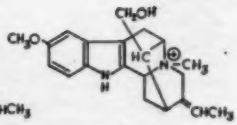
C-Alkaloid Y [13]



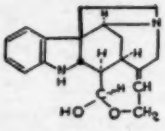
C-Fluorocurarine [36-39]



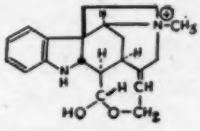
Lochnerine [29]



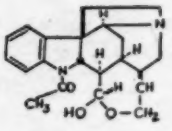
Lochneram [22]



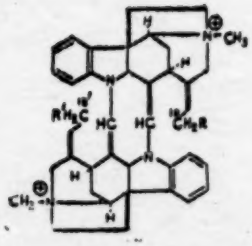
Caracurine VII = Wieland-Gumlich-aldehyde [33,34]



N(b)-Metho-Wieland-Gumlich-aldehyde = C-Alkaloid A8 [15]

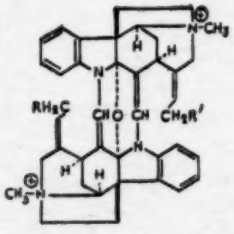


Diaboline = N(a)—Acetyl-Wieland-Gumlich-aldehyde[35]

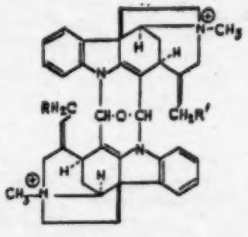


R = R′ = H: C-Dihydrotoxiferine [40-42,47]
R = H; R′ = OH: C-Alkaloid H[43]
R = R′ = OH: C-Toxiferine [41]

(a)

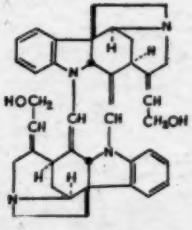


(b)

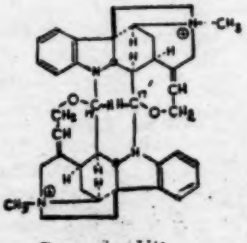


R = R′ = H: C-Curarine[44]
R = H; R′ = OH: C-Alkaloid G[43,44]
R = R′ = OH: C-Alkaloid E[44]

} Formula (a) or (b)



Caracurine Va = Nor-C-toxiferine [15,41]



Caracurine V[41]

Alkaloids isolated from Calabash curare *and* Strychnos barks.

Quaternary alkaloids. Names.	Isolated from Calabashes.	Strychnos barks[a].	Empirical formulæ[b].	Colour reaction with Ce^{IV} sulphate+conc. H_2SO_4 immediately/after 5-10 sec.	R_C[c] developed with solvent C[c].	R_B[d]	HD[f] in μ/kg. mice.	Isolation.
C-alkaloid A	+	Mi	$C_{40}H_{48}O_4N_4^{++}$	blue violet/orange	0.23		7	3,4
C-alkaloid B	+	Mi	$C_{40}H_{46}O_2N_4^{++}$	red violet/colorless	0.34		280	3,4
C-alkaloid C	+	Mi, sol	?	red violet/ ,,	0.34		240	3,4
C-alkaloid D	+	Mi, sol	$C_{40}H_{48}O_2N_4^{++}$	red violet/ ,,	0.35		1100	3,4
C-alkaloid E	+	tom, sol, Fro	$C_{40}H_{44}O_3N_4^{++}$	blue/ light green	0.36		0.3	3,4
C-toxiferine I (=Toxiferine I)		*tox*, tom, Fro	$C_{40}H_{46}O_2N_4^{++}$	red violet/colorless	0.42		9	5
C-alkaloid F	+	sol	$C_{40}H_{48}O_3N_4^{++}$	red violet/orange	0.49		75	3,4
Toxiferine VIII		*tox*	—	—	0.63			45
C-alkaloid G	+	sol	$C_{40}H_{44}O_2N_4^{++}$	blue/light green	0.65		0.6	3,4
C-alkaloid R	+		$(C_{21}H_{27}O_2N_2)^+{}_x$	violet	0.68			6
C-alkaloid H	+	tri, sol	$C_{40}H_{46}ON_4^{++}$	red violet/colorless	0.71		16	3,4
C-alkaloid BL	+		$C_{40}H_{30}O_2N_4^{++}$?	blue/blue green	0.75		455	7
C-calebassine(=Toxiferine II =C-strychnotoxine I)	+	tri, div, sol, Mi, rub	$C_{40}H_{48}O_2N_4^{++}$	blue violet/orange	0.80		240	8,9
C-alkaloid-I	+	tri, Fro, rub	$(C_{20}H_{23-25}N_2)^+{}_x$?	blue violet/red	0.89		174	3,4
C-curarine-I	+	tri, div, tom, sol, Mi, gu	$C_{40}H_{44}ON_4^{++}$	blue/light green	1.00		30	9,10
C-alkaloid J	+	Fro	?	pale red violet/colorless	1.04		290	3,4
C-guaianine	+		$(C_{20}H_{25}ON_2)^+{}_x$?	blue violet	1.12		35	11
C-dihydrotoxiferine (=C-alkaloid K)	+	Fro, tri	$C_{40}H_{46}N_4^{++}$	red violet/colorless	1.22		30	3,8,12
C-alkaloid M	+		$(C_{20}H_{23}O_2N_2)^+{}_x$?	none/yellow (20′)	1.45		4.5 mg. inefficient	13,14
Alkaloid A8 (=N(b)-metho-Wieland-Gumlich-aldehyde)		*tox*	$C_{20}H_{23}O_2N_2^+$	orange	1.50			15,45
C-alkaloid Y(=Profluorocurine)	+		$C_{20}H_{27}O_2N_2^+$	red violet	1.59		—	13
C-calebassinine	+	sol	?	carmine /, light brown	1.68		22000	3,4
Fedamazine	+	*tox*	$C_{20}H_{21}ON_2^+$	blue	1.90		2000	16
C-fluorocurine	+	*tox*, tom, sol, Mi, *mel*, sub	$C_{20}H_{23}O_2N_2^+$	orange	2.10		4400	17,45

(Contd.)

C-fluorocurine + *tox*, tom, Mi, Fro, *mel*, sub

(Contd.)

Quaternary alkaloids. Names.	Isolated from Calabashes.	Isolated from Strychnos barks[a].	Empirical formulæ[b].	Colour reaction with Ce^{IV} sulphate + conc. H_2SO_4 immediately/after 5-10 sec.	R_C[c]. developed with solvent C[c].	R_B[d].	HD[f] in μ/kg. mice.	Isolation.
C-pseudofluorocurine	+	—	$C_{20}H_{25}O_2N_2^+$	red/orange	2.10			6
C-fluorocurinine	+	tri, tom, Mi, Fro, rub	?	carmine/wine red	2.23		2750	3,4
C-fluorocurarine (=C-curarine III)	+	tri, div, tom, sol, Mi, rub, sub	$C_{20}H_{23}ON_2^+$	pale blue	2.25		1800	3,4,18
Toxiferine XII		*tox*	?	—	2.30			45
C-alkaloid L	+		?	red	2.50		1900	3,4
C-mavacurine	+	*tox*, *mel*, rub, div, Mi, Fro, am, sub	$C_{20}H_{25}ON_2^+$	carmine	2.70		—	13,19
Melinonine A(=N-metho-py-tetrahydro-alstonine)		*mel*	$C_{22}H_{27}O_3N_2^+$	none		1.46	—	20,21
Melinonine B		*mel*	$C_{23}H_{27}ON_2^+$	,,	2.72	1.00	—	20,21
Melinonine E		*mel*	$C_{20}H_{23-25}ON_2^+$	,,		0.86	—	21
Melinonine F (=Harman-N(b)-methosalt)		*mel*	$C_{13}H_{13}N_2^+$	,,		0.74	—	21
Melinonine G (=flavo-pereirine)		*mel*	$C_{17}H_{15}N_2^+$	,,		1.15	—	21
Melinonine H		*mel*	$C_{20}H_{21-23}ON_2^+$			0.54	—	21
Melinonine I		*mel*	?	yellow brown		0.74	—	21
Melinonine K		*mel*	?	,,		0.56	—	21
Melinonine L		*mel*	$C_{20}H_{26}O_4N_2$	pale blue		—	—	21
Melinonine M		*mel*	?	none		—	—	21
Macusine-B		*tox*	$C_{20}H_{25-27}ON_2^+$	pale grey	3.00		—	45
Lochneram	+		$C_{21}H_{27}O_2N_2^+$	none/yellow (after 20')	3.10		—	22
Macusine-A		*tox*	$C_{22}H_{27}O_3N_2^+$	pale grey	3.60		—	45
C-alkaloid O	+		$C_{20}H_{27}ON_2^+$?	none (in 50% H_2SO_4+ Ce^{IV} sulphate: blue green)	3.95		7000	11
C-alkaloid P	+		$C_{20}H_{23}ON_2^+$?	blue			2500	11
C-alkaloid X	+		?	orange/red (1-2[h])			—	17
C-xanthocurine	+		$C_{20}H_{21}ON_2^+$	blue green			620	11

(Contd.)

Quaternary alkaloids. Names.	Isolated from Calabashes.	Strychnos barks(a).	Empirical formulæ(b).	Colour reaction with Ce^{IV} sulphate + conc. H_2SO_4 immediately/after 5-10 sec.	R_C(c) developed with solvent C(e).	R_B(d).	HD(f) in μ/kg. mice.	Isolation.
Toxiferine II (=Strychnotoxine II(g)	+	*tox*	?				—	8
Toxiferine I(h)		*tox*	?				—	5,23
C-isodihydrotoxiferine	+		?				—	8
C-curarine II(=Strychnotoxine I_a)	+		?				—	18
Alkaloid 1	+		?				—	19
Alkaloid 2	+		?				—	19
l-Curine	+		?				—	18
Alkaloid γ		am	?					24
Macrophylline A		ma	?				—	25
Guiacurarine III		gu					—	26
Tertiary alkaloids								
nor-Dihydrotoxiferine		*tox*	$C_{38}H_{40}N_4$	violet/orange				16,27
Caracurine I		*tox*	?	purple/brownish	0.7		2000	16,27
Caracurine II		*tox*	$C_{38}H_{38}O_2N_4$	purple/bownish	0.8		>16,000	16,27
Caracurine III		*tox*	?	purple/brownish	0.8		>15,000	16,27
Caracurine IV		*tox*	?	violet/orange brown	1.0		330(k)	16,27
Caracurine V		*tox*	$C_{38}H_{40}O_2N_4$	purple/brown	1.4		700(k)	16,27
Caracurine VI (=nor-C-alkaloid H)		*tox*	?	purple/brown	1.6			
Caracurine VII (=Wieland-Gumlich-aldehyde)		*tox*	$C_{19}H_{22}O_2N_2$	orange	2.1		1140(k)	16,27
Caracurine VIII(i)		*tox*	?	purple/brown	1.4		1020(k)	16,27
Caracurine IX(i)		*tox*	?	red violet/violet brown	1.1		1050(k)	16,27
Diaboline (=N(a)-acetyl-Wieland-Gumlich-aldehyde)	+	*dia*	$C_{21}H_{24}O_3N_2$	none			—	28
Lochnerine (C-alkaloid T)	+	*Lochnera rosea* (L.)	$C_{20}H_{24}O_2N_2$	light pink			—	29
C-alkaloid Q	+		$C_{22}H_{27}O_3N_3$?	none	4.92(l)		—	6
C-alkaloid S			$C_{19-20}H_{22-24}N_2$?	red violet	0.51(m)			6

(Contd.)

Glossary:

(*c*)	Mi	= Str. Mitscherlichii	div	=	Str. divaricans Ducke
	sol	= Str. solimoesana Kruk.	rub	=	Str. rubiginosa DC.
	tom	= Str. tomentosa (Benth.)	gu	=	Str. guianensis (Aubl.) Mart.
	Fro	= Str. Froesii Ducke	mel	=	Str. melinoniana Baill.
	tox	= Str. toxifera Rob. Schomb.	am	=	Str. amazonica Kruk.
	tri	= Str. trinervis (Aubl.) Mart.	sub	=	Str. subcordata Spruce.

Abreviations indicated by italics signify that the alkaloid has been isolated, in the other case the alkaloid was only demonstrated by paper chromatography.

(*b*) Doubtful formulas are designated with ?

(*c*) R_C = migrational distance of the alkaloid chloride relative to the migrational distance of C-curarine-I-dichloride.

(*d*) R_B = migrational distance of the alkaloid chloride relative to the migrational distance of melinonine-B-chloride.

(*e*) Solvent "C" = methylethylketone saturated with water containing 1-3 vol.% methanol.
Solvent "D" = ethyl acetate-pyridine-water (7.5:2.3:1.65).

(*f*) "Head-drop" -dosis in μ/kg. mice.

(*g*) Perhaps identical with C-alkaloid A.

(*h*) Perhaps identical with C-toxiferine I.

(*i*) Isolated as chloromethylate.

(*k*) HD-dosis of the respective chloromethylates.

(*l*) R_C-value with solvent "D".

(*m*) R_C-value with solvent "D" = 1.35.

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The Nitration of Some Catechol and Quinol Derivatives

R. Robinson

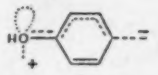
The reactions indicated by the title are in the class of those between electron-donating and electron-accepting entities, the phenolic-derivative component being in the former category.

This view of the reactive character of phenols (and incidentally of aromatic amines) was first adumbrated in 1916 by Hamilton and the writer[1], who extended it in several directions including the representation of the reactivity of pyrrole and of such substances as ethyl β-aminocrotonate[2].

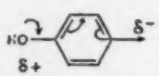
The symbolism was by a system of partial valencies. In the following year a modification differing from Thiele's was introduced, in that the partial valencies were derived from the normal valencies by division[3]. This seemed a small point at the time but it was really of vital importance since the translation into electronic terms became feasible and, indeed, quite obvious. The reaction process was envisaged as a coherence by the part valencies and it was stated that this would be followed by a movement of electrons along potential gradients[2].

The electronic theory of chemical binding was clearly implied by Sir Joseph Thomson[4], for example in his Silliman Lectures of 1903, but it was developed in a much more precise form by G. N. Lewis[5] from 1913, especially in 1916, and in his "Valence and the Structure of Atoms and Molecules" which was published in 1923.

The writer realised that Lewis' theories could be used to directly interpret his own part-valency symbols and developed this idea in lectures from 1919-1921. The translation was published in 1922 with W.O. Kermack and the symbol ↷ was then introduced in order to indicate certain electron displacements. The example of activated phenol will illustrate the close relationship between the two systems.

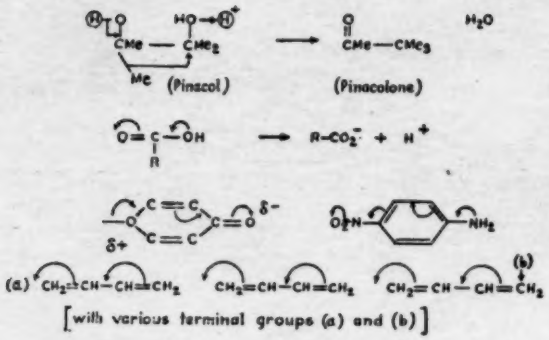


Phenol with partly dissociated valencies.



Phenol polarized by electronic displacement.

The new representation of conjugation and conjugative electron displacement of all types threw a flood of light on the theory of organic chemical reactions and embraced the most diverse topics, for example, orientation in substitutions and intramolecular rearrangements. The characters of carboxyl groups and their derivatives received natural explanations, and the broad mechanism of polymerisation became self-evident[7].



The theory has stood the test of almost 40 years and has not been modified in essential respects. It has, however, been itself explained and refined in terms of modern wave mechanics with the result that some quantitative results have emerged.

It is hardly possible to open a monthly part of a ny Journal devoted to organic chemistry without finding applications of these ideas and Professor Sir Christopher Ingold and his school have been among the most active of those who have adopted them and used them to most useful purpose in the study of reaction mechanism. It is accordingly surprising that Sir Christopher Ingold has allowed himself to state that the writer's ideas were 'devoid of any physical basis'[8]. If that is so, the same disparagement must apply to the applications of these theories published so widely over the last four decades and in particular to a great part of his own work and that of his associates.

Actually the physical basis is a simple one, namely that electronic displacements in conjugated systems can only occur in such a manner as to preserve the electronic configurations of the atoms concerned to the maximum possible extent. By 'electronic configuration' we mean the *number* of electrons associated with the respective atoms. Furthermore, it is clear that on polarisation one of the atoms will be in electron defect but none of them can acquire an electron excess in terms of the number of associated electrons. There will nevertheless be a negative electric charge on one atom. For example, in

$$CH_2=\overset{\curvearrowright}{C}H_2 \qquad \text{to} \qquad \overset{\delta+}{C}H_2=\overset{\delta-}{C}H_2$$

the δ^- charge results from a change of sharing. The symbols δ^+ and δ^-, like some other examples of acceptable nomenclature, are due to Ingold. Another such suggestion is that of 'nucleophilic' and 'electrophilic' instead of Lapworth's 'anionoid' and 'cationoid' respectively without, however, any change of meaning.

Whilst continuing to use these alternative terms, it should be mentioned parenthetically that the coulombic forces may not be the only ones controlling the direction taken by chemical change. Coupling of electrons of opposite spin may also exert an important influence on orientation, especially when the much larger coulombic forces are balanced. A legacy of the origin of the electronic theory of polarisation of simple and conjugated systems in partial valency ideas was the insistence on graded separation of the charges. The curved arrows indicated displacements of unspecified values and the formation of an ion pair is simply the extreme case. This was later put forward by Lowry as if it were a new conception. His suggestion that a double bond is made up of one

co-valency and one electro-valency was criticised by Lapworth and the writer at the time[9] and the following passage from our note may be cited.

> "There are theoretical difficulties also, and even a certain doubt as to what the theory of 'mixed double bonds' really implies. The remark that *a double bond in organic chemistry usually reacts as if it contained one covalency and one electrovalency* is, with its double qualification, unexceptionable, being no more than a restatement of the fact that unsaturated compounds undergo polar additive reactions—sometimes. It might, of course, be taken to imply a readiness to accept the theory of 'activated molecular phases,' which the present writers in most cases employ, but this is not clear, and in all the remainder of the paper from which the quotation[10] has been taken definite electrovalencies are allotted to all unsaturated compounds. Indeed, this adoption of completely polarised unsaturated linkages is what confers novelty on Professor Lowry's views, and at the same time it is the feature of them to which we take exception. It should be mentioned that graded electrovalencies appearing in activated molecules, and possibly in normal molecules containing carbonyl and similar unsymmetrical groups, were postulated by both of us prior to the appearance of Professor Lowry's papers."

The last sentence of this citation has been included in order to stress the fact that simple and conjugative electronic displacements were from the beginning assumed in normal molecules and not necessarily those activated in some way, or in course of reaction. This idea was always emphasised in teaching and in lectures in various centres. An example of its use is the conception of neutralised systems. Thus amides were assumed to owe their properties to theoccurrence of the displacements, $^{\delta+}\!-\!N\!-\!C\!=\!\overset{\frown}{O}\,^{\delta-}$, which 'neutralise' to varying degrees in different cases, the basic character of the N and the cationoid character of the C and with formation of a dipole which can be experimentally observed.

As these properties refer to the normal molecular species, it would be meaningless to suppose that the electronic effects, which produce them, are not also characteristic of the resting molecules. Once again Ingold introduced a new name for this phenomenon, namely 'mesomerism' but it described an idea which had already been advanced.

On the side of the nitrating reagent it has been plausibly argued, with support from kinetic data, that, at least in sulphuric acid solution, the effective entity is the nitroxyl ion NO_2^+[11]. Certainly this must be a powerfully reactive cation and an example where the theory applies is probably the nitration of *m*-dinitrobenzene to *s*-trinitrobenzene by a cold mixture of absolute nitric and perchloric acids. Even a mixture of nitric and sulphuric acid (or oleum) will not achieve this result at the room temperature. The observation was made by Georg Müller working on the roof of the Dyson Perrins Laboratory. But these are extreme conditions—a very resistant substrate and a reagent in which nitroxyl ions must be present. Many nitrations occur under much milder conditions and the writer cannot accept a generalisation of the nitroxyl ion hypothesis. It seems much more probable that $HO^{\delta-}\ldots NO_2^{\delta+}$ is effective in concerted processes. The grades occurring in nitration probably reflect the existence of threshold degrees of separation of the charges. Indeed it is hard to believe that they have any other explanation. Thus $H^+\}NO_3^-$ is not a nitrating agent; HNO_3 nitrates when δ^+ in $HO.\,NO_2^{\delta+}$ reaches a certain value. It must reach a higher value in order to make certain more difficult reactions feasible, and so on. Finally NO_2^+ is the most effective entity.

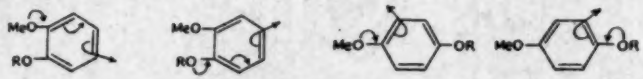
The nitration of veratrole (and of quinol dimethyl ether) proceeds in clearly defined stages and yields a single product in each case. In acetic acid solution (less cleanly if the

medium is aqueous) little more than one mole HNO_3 suffices to convert veratrole into 4-nitro-1, 2-dimethoxybenzene. The presence of the 3-nitro derivative has never been demonstrated and neither has a dinitro derivative been isolated. Ordinary concentrated nitric acid (*d*, 1.42) converts the mononitro compound into 4,5-dinitro-1,2-dimethoxybenzene and no trinitro derivative is obtained. The latter, viz., 3,4,5-trinitro-1,2-dimethoxybenzene is produced in a mixture of nitric and sulphuric acids. All three stages can be accomplished at room temperatures. The nitration of 1, 4-dimethoxybenzene proceeds analogously.

The quantitative character of the mono-nitration was particularly attractive because it offered a reliable means of experimental study of electronic displacements and especially a good opportunity to observe the interaction of the conjugative (electromeric) displacements and the field, inductive, or general effects. The latter were already an established part of chemical theory. For example, in explaining the data regarding the relative strengths of acids.

Lucas[12] was the first to relate this 'general' effect to orientation in additions to substituted olefines. He did not, however, distinguish between the 'general' and 'electromeric' processes and, even if this can be justified for simple systems, it is necessary in more complex cases to consider the two types of displacement separately.

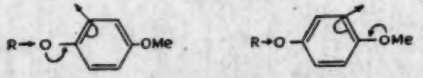
In the cases of the catechol and quinol ethers, the existence of two hetero-enoid systems is postulated, denoted by A and B, leading to attack by the nitrating agent in corresponding positions as indicated below.



(A) (B) (A) (B)

In all cases one of the alkyloxy groups was CH_3O (the A-system) and R in OR (the B-system) was a higher alkyl or alpharyl group. The ratio of the products produced could be determined, with little experimental error, by means of the thermal behaviour of mixtures of the components synthetically prepared and this ratio may be taken as a measure of the relative orientating powers of the groups OR with respect to OMe. Conveniently the orientating power of OMe was taken as 100. This method of comparison, in which the two groups examined are in one and the same molecule, avoids some pitfalls of the alternative method (study of a series XOMe.....XOR)because it is clear that dubieties, caused by changes of molecular weight including varied degrees of association of the molecules, and other changes connected with passage from one molecular species to another, are automatically avoided. On the other hand, there are not many examples to which this method can be applied. The fundamental idea of the work was that R in ·OR should have a general or inductive effect different from that of Me in ·OMe and that this general effect will promote or retard the displacements in the system starting with OR, relative to those including OMe. If R is a higher alkyl group, then we expect the electron density round O to be *increased*, resulting in an increased displacement in the B system and greater reactivity of that system. In other words, an increase in the orientating power of OR.

Considering first the quinol derivatives, we have the circumstances illustrated below.



(B) Facilitated by R→·O (A) Hindered by R→·O

It is generally assumed that the inductive effect operates both through the chain and more generally through space (field effect). Either way an increased electron release by R towards O will augment the reactivity of the B-system but *oppose* that of the A-system. This consideration is exemplified in the above diagram which shows that an electron release by R in the direction of the nucleus must diminish the displacement in the A-system. Thus the disparity of OR and OMe in orientating power should increase with the electron release by R. This field effect may be small in the quinol series, due to the relatively large distances involved, but it is important in the catechol series as shown below.

The orientating powers found in the quinol methyl alkyl ether series[13] were:—MeO, 100; $CH_3.CH_2.O$, 163; $CH_3.CH_2.CH_2.O$, 180; $CH_3.CH_2.CH_2.CH_2.O$, 186; n-$C_{16}H_{33}.O$, 212. This steady rise in the normal chain series favours the idea of a consistent electron release on replacement of H by CH_3 as indicated by the symbol $CH_3 \rightarrow C$. In the branch-chain groups we anticipate a much larger effect due to the proximity of the source and in accordance with electrostatic principles.

This is seen in the example $CH_3.CH_2.CH_2.O$, 180; $(CH_3)_2CH.O$, 229; and $CH_3.CH_2.CH_2.CH_2.O$, 186; $(CH_3)_3C.O$; 328[14].

Thus in the quinol dialkyl ether series, *t*-butyloxy has more than three times the orientating power (nitration) of methoxyl. These figures take no account of steric hindrance which, in view of the *o*-substitution, should operate against the reactivity of the systems including the larger groups. This effect is evidently of minor importance in the case under consideration.

In the catechol ether series, any part of the inductive effect of R, displacing electrons towards the aromatic nucleus, which is a field effect, will tend to activate MeO to some extent.

The disparity between OR and OMe will accordingly be less in this series[15] than in the quinol derivatives. Thus EtO (quinol), 163; EtO (catechol), 135. Furthermore *n*-BuO (quinol), 186; *n*-BuO (catechol), 128. The latter value is actually lower than that for EtO, showing that the distributed field effect has become quite important and has greatly reduced the disparity between RO and MeO.

The method enables us to study the relative inductive effects of other groups.

In the quinol series $Ph.CH_2.O$, 107; p-$NO_2.C_6H_4.CH_2.O$, 38; indicating a small electron repulsion by Ph replacing H and an electron attraction by $NO_2.C_6H_4$. In the catechol ether series m-$Cl.C_6H_4.CH_2.O$, 69, and p-$Cl.C_6H_4.CH_2.O$, 82,[16] exhibit the electron attraction due to Cl; it may be predicted that these values would be found to be lower in the quinol series.

The values for *m*-and *p*-nitrobenzyloxy were found to be about equal (67) and the high value for *p*-chlorobenzyloxy was attributed to the effect of conjugation $Cl\overset{\frown}{—}C_6H_4—$ which would clearly be more effective from the *p*- than from the *m*-position.

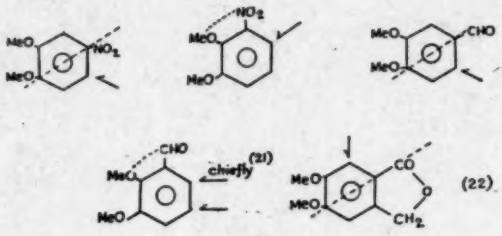
In the quinol series PhO has a very weak orientating power since $PhO.C_6H_3$ (OMe)-NO_2.(O-) was the only isolable product[17].

An investigation was also carried out among some of the derivatives of *p*-aminophenol and the results could be interpreted along similar lines[18]. The *p*-nitrobenzoylamino group had about twice the orientating power of ethoxyl, the *m*-nitrobenzoylamino group was a little more powerful and the *o*-nitrobenzoylamino group was less powerful. All are

much less powerful than the benzoylamino group, the results with which varied somewhat on the use of different concentrations of nitric acid.

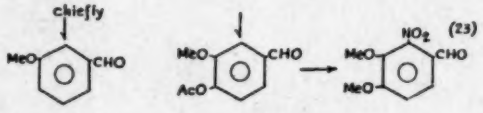
A few other phenomena encountered in the study of nitration of catechol derivatives may be briefly mentioned.

When one group –OR is partly neutralised by *o*-or *p*-carbonyl or nitro groups, the second OR is the one included in the more active hetero-enoid system. The following examples illustrate the point [19]. The circle symbolises the aromatic sextet [20]; it is inconvenient to write Kekule formulae where complex conjugative effects are to be represented.



(← indicates the point at which substitution occurs).

For the synthesis of methoxylated phenanthrenes, which, were obtained from codeine and thebaine, a source of 2-nitroveratraldehyde was needed. As seen above, direct nitration of veratraldehyde gives the 6-nitro derivative. Use was made of a peculiar orientation phenomenon, namely that, in many cases, when *op*-and *m*-directive groups are in the *m*-position to one another, nitration occurs between the two groups. For example:



By hydrolysis and methylation the nitro-acetylvanillin afforded 2-nitroveratraldehyde.

Lastly, there is no very satisfactory explanation for the exclusive nitration of veratrole in the 4-position, or of pyrogallol trimethyl ether in the 5-position.

The arrows in these expressions are only direction signs. Probably this phenomenon is one that could be explained by overlapping orbitals; it is not easy to comprehend by use of the simple electronic conceptions which are quite satisfactory for most purposes.

These fields have been chosen for the present purpose because there is much scope for further work along the lines indicated. Especially, further comparisons of RO and MeO in the catechol and quinol series would be of great value.

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Recent Progress in Synthetic Dyes

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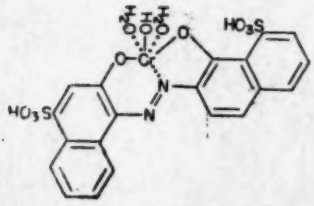
The second edition of the Colour Index, published in 1956-58 by the Society of Dyers and Colourists, Manchester, and the American Association of Textile Chemists and Colorists, lists 4702 dyes and allied products, classified both according to their usage and their chemical constitution. The dyes in the former classification are more numerous, because there are many commercial dyes, the structures of which have not been disclosed. In fact, there are very few dyes indeed for which the constitution is given in the new Colour Index and not in a 1952 publication[1,2] in which it was possible to include the structures of numerous commercial dyes because of the information on the German dyestuff industry which became available after the second world war in BIOS and FIAT reports. For reasons which are not easy to understand, dye manufacturers, unlike the manufacturers of synthetic drugs, are reluctant to reveal the chemical constitution of their products. Nevertheless, it is clear from patents and from publications in which broad structural features are indicated in connection with dyeing properties that there has been no slackening of the search for new synthetic dyes. Comprehensive accounts of progress year by year in the chemistry, technology, and application of colouring matters appear in Reports on the Progress of Applied Chemistry and Review of Textile Progress; and only a few of the developments during the last ten years, chosen somewhat arbitrarily, are outlined in this brief survey.

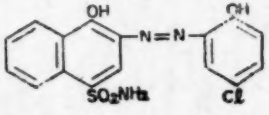
Azo Dyes

An important addition to the literature of dyestuff chemistry is a book by Zollinger[3], who in recent years has materially advanced our knowledge of the diazonium coupling reaction by studying the kinetic isotope (deuterium) effects.

The application of mordant azo dyes was greatly facilitated by the production of water-soluble dyes containing the metal (usually chromium) in co-ordination (Neolan dyes, Ciba; Palatine Fast dyes, I. G.). These were of the type (I) in which the complex contained one atom of chromium and one molecule of the azo dye. The dyeing process had one disadvantage that it involved the use of relatively high concentrations of sulphuric acid.

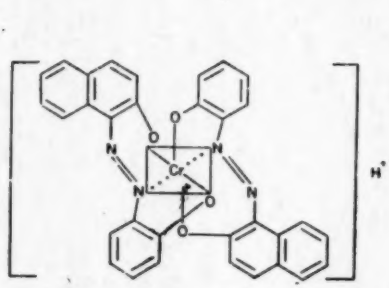


(I)

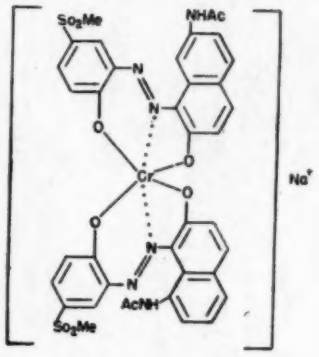


(II)

The I. G. first marketed neutral-dyeing metal-dye complexes, such as the blue chromium complex of (II), in which the azo dye contained one or more sulphamyl instead of sulphonic groups. Several of the Perlon Fast dyes, special dyes for synthetic polyamide fibres, were of this type[1]. The water-solubility, however, was unsatisfactory. The Geigy Co. then made the discovery that a 2:1 complex of dye and chromium of the type (III), described by Drew and Fairbairn in 1939, fulfilled the requirements for neutral dyeing; the complex (III) is a monobasic acid, which forms a monosodium salt, and the water-solubility is increased to meet the needs for practical dyeing by the introduction of $-SO_2Me$ and similar groups[4]. Such dyes are now offered by all the leading dye manufacturers, and an example[3] is Irgalan Grey BL (IV).



(III)



(IV)

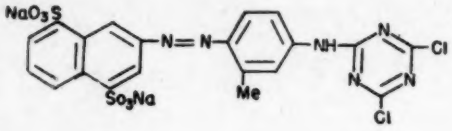
Japanese and Russian workers are investigating the relation between the constitution of azo dyes and their absorption spectra, dyeing, and fastness properties. In a series of interesting papers B. I. Stepanov has shown that chlorine in *o*-chloro-*o'*-hydroxyazo compounds or in 8-chloro-2'-hydroxyazonaphthalenes can be replaced by an alkoxy or phenoxy group by heating the copper complex (prepared separately or *in situ*) with sodium alkoxide or phenoxide in toluene.

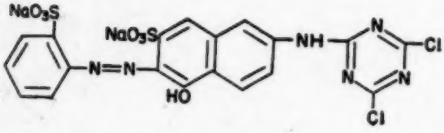
The general method for determining the structure of azo dyes is to reduce them under neutral, acid, or alkaline conditions and identify the arylamines and their sulphonic acids thus obtained. The isolation of arylamine sulphonic acids from aqueous solution and their characterization have been facilitated by chromatographic methods. Conversion of the arylamines, phenols, and their sulphonic acids to the coloured 2,4-dinitrophenyl derivatives, or into condensation products with cyanuric chloride, which are further treated with dimethylamine, offers advantages and is under investigation[5].

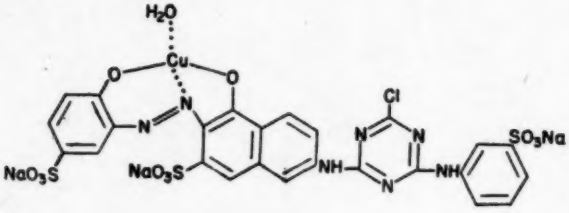
Reactive Dyes for Cellulose

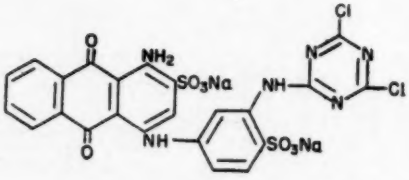
The use of cyanuric chloride for linking two or three molecules of the same or different dyes containing free amino groups has been the subject of numerous patents, mainly of the Ciba Co., and the first account of the preparation and properties of the cyanurated dyes was given by Fierz-David and Matter in 1937. A recent development, which represents a landmark in the history of synthetic dyes, is the application of dyes of the type (V),

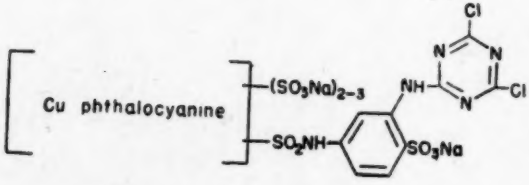
which are capable of entering into stable chemical combination with cellulose in presence of alkali, unlike the known dyes for cellulose fibres which attach themselves to the cellulose macromolecule by hydrogen bonding and/or van der Waals' forces. The Procions (I.C.I.) and Cibacrons (Ciba) are such "reactive" dyes. The structures of Procion and Cibacron dyes are illustrated by (V), (VI) (VII), (VIII) and (IX).

(V)  Yellow

(VI)  Orange

(VII)  Rubine

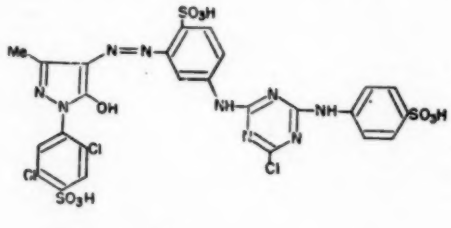
(VIII)  Blue

(IX)  Blue

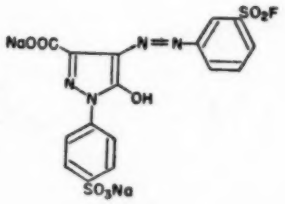
The yellow to red dyes are monoazo; the blues are derivatives of 1-amino-4-anilinoanthraquinone-2-sulphonic acid or phthalocyanine; and the greens are mixtures or condensation products of blue and yellow dyes. Lack of substantivity is regarded as an advantage, because any dye, substantively adsorbed but not chemically combined with the fibre, will lead to poor wash fastness. Thus the dyes are constituted like typical acid dyes and do not possess the structural features characteristic of direct cotton dyes. The new Colour Index lists only three azo dyes derived from cyanuric chloride (Colour Index 34040; 34045; 28500); the first two (Coprantine Green G and Chlorantine Fast Green BLL) contain no

chlorine attached to the triazine ring and are therefore unreactive dyes; the last (Chlorantine Fast Blue 8G) has one chlorine free, but is not applied as a reactive dye. The second and third chlorine atoms in the triazine ring react with some of the primary alcoholic groups in cellulose. The dichlorotriazines, such as (V), to which type most of the Procions (other than the Procion H brand) belong, react with cellulose in presence of sodium carbonate at room temperature or by warming; a secondary reaction, which can take place with the dichlorotriazines, is cross-linking of the cellulose chains, rendering the dyed fibre insoluble in cuprammonium hydroxide solution[6]. The monochlorotriazines, such as (VII), representing the Procion H and Cibacron dyes, require a higher temperature as well as a stronger base for interaction with cellulose; their greater stability also results in less decomposition on storage.

Wegmann has studied the relation between constitution and dyeing properties of the reactive dyes derived from cyanuric chloride[7]. The structures of some of the Cibacron dyes have been determined by Panchartek *et al*[8]. Two examples are Cibacron Brilliant Yellow 3G (Procion Brilliant Yellow H5GS; X) and Cibacron Brilliant Blue BR (VIII in which one chlorine is replaced by metanilic acid). Bao-Chi-Min has synthesized a series of such dyes and examined their fastness properties[9].



(X)



(XI)

The success of the Procion and Cibacron dyes has led to a search for dyes containing reactive halogen in other heterocyclic rings such as pyrimidine and phthalazine or in simpler groups such as sulphonyl fluoride. Thus the dye (XI), fixed on the cotton fibre with acid-binding agents, gives greenish yellow shades which are fast to light and washing. Krazer and Zollinger[10] have shown that the dyed fibre is a sulphonic ester, in which the dye is replaced by iodine on treatment with sodium iodide in acetone. This reaction is specific for dyes containing SO_2F groups; and other methods for characterizing the dye-fibre bond, such as microbiological degradation, isotope technique and solubility tests, have been discussed by Zollinger.

In the Remazol dyes of B.A.S.F., which also combine with cellulose by covalent bonds, the interaction depends on a different mechanism. The dyes are of the general type $D\text{-}SO_2CH_2CH_2OSO_3Na$, in which D is a dye molecule[11]. When a Remazol is applied to cotton or viscose by a printing process or by dyeing at 60° in presence of sodium carbonate, it decomposes to a vinyl sulphone ($D\text{-}SO_2\text{-}CH\text{-}CH_2$), which then combines with cellulose to form compounds of the type $D\text{-}SO_2\text{-}CH_2CH_2\text{-}O\text{-}Ce$. The reactivity of the Remazols appears to lie between the monochloro- and dichlorotriazines. The Remazols now available are mainly suitable for printing. Dyes containing the group $-NHCOCH_2CH_2Cl$ probably react via the acrylamide $-NHCOCH{=}CH_2$. Isocyanate and other groups capable of interaction with alcoholic hydroxyl groups are potentially useful in the synthesis of reactive dyes, but the general problems are (*a*) their application to fibres under practical dye-

ing conditions, keeping the competitive reaction with water or aqueous alkali to a minimum, and (*b*) the removal of dye not combined with cellulose by a simple washing treatment which does not break the ester-type cellulose-dye bond.

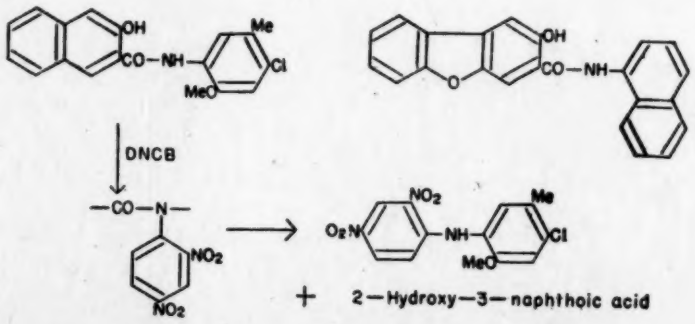
The Procions and other 'reactive' dyes are by no means free from technical disadvantages such as instability on prolonged storage and loss of colour in the dyebath for the obvious reason that the reactive chlorine atoms can combine with water as well as with the hydroxyl groups of cellulose. These doubtless have great possibilities in dyeing and printing cellulose fibres, but there is no reason to believe that they threaten in any way the future of the well established azoic and vat dyes, which have much higher fastness to washing.

Azoic Dyes

Naphtol AS-FGGR, a phthalocyanine derivative, is mentioned later. The structures of eight Naphtols, not mentioned in the 'Chemistry of Synthetic Dyes', are disclosed in the new "Colour Index". Five of them are simple derivatives of 2-hydroxy-3-naphthoic acid, described in old patents or publications[12]; AS-AN is the *p*-nitroanilide, AS-MCA the *m*-chloroanilide, AS-AM the *m*-4-xylidide, AS-KB the 2-methyl-5-chloroanilide, and AS-BM the *o*-tolidide. Naphtol AS-BI is the *o*-anisidide of 6-bromo-2-hydroxy-3-naphthoic acid[13]. The yellow-producing Naphtols AS-IRG and AS-IFG are 4-chloro-2,5-dimethoxyacetoacetanilide and benzoylacet-4-benzamido-2,5-dimethoxyanilide; they are suitable for printing, but do not possess adequate substantivity for use in dyeing[14].

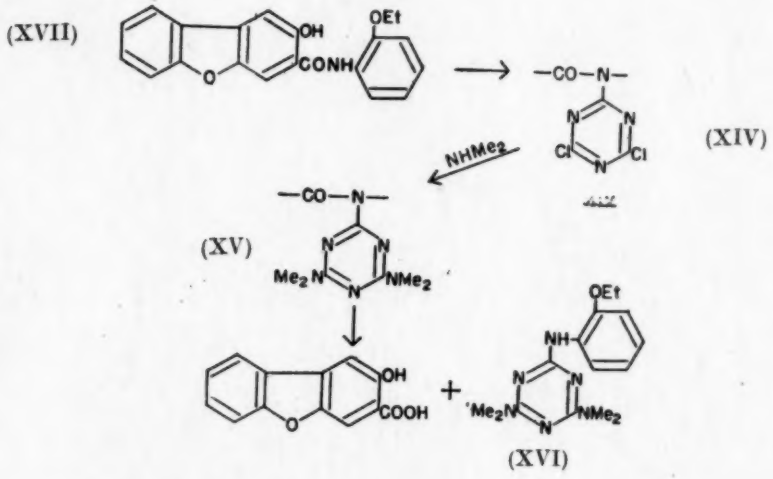
Only one new Fast Base (diazotizing component) is mentioned in the new Colour Index: Fast Red Base PDC, which is the *n*-butyl amide of 3-amino-4-methoxybenzenesulphonic acid.

An interesting reaction of *o*-hydroxybenzamides, useful for the hydrolysis of Naphthols and identification of the acid and amine components, is their behaviour towards cyanuric chloride and 2,4-dinitrochlorobenzene, both of which attack the amide nitrogen and not the phenolic hydroxyl group[15]. The reaction appears to proceed by a direct displacement of the halogen by the amide nitrogen involving intramolecular nucleophilic catalysis by the phenoxide oxygen; but a Smiles rearrangement is not completely excluded. The *N*-dinitrophenyl derivatives are stable to boiling hydrochloric acid, but are hydrolysed easily by aqueous sodium carbonate or hydroxide. Thus Naphtol AS-RS and AS-KN have been shown to be the 4-chloro-2-methoxy-5-methylanilide (XII) of 2-hydroxy-3-naphthoic acid and the ∝-naphthylamide (XIII) of 3-hydroxydibenzofuran-2-carboxylic acid respectively.

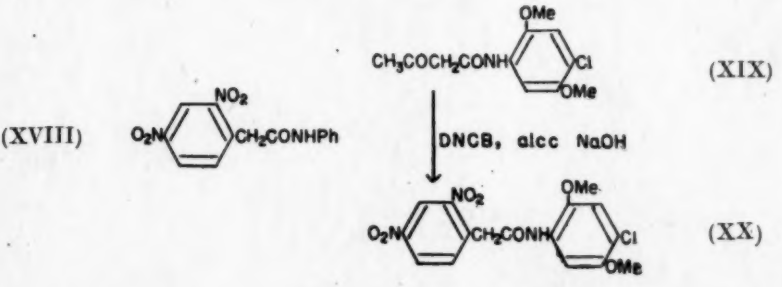


(XII) (XIII)

Mild alkaline hydrolysis of the *N*-dinitrophenyl derivative of a Naphthol leads readily to the brightly coloured and easily crystallizable dinitrodiphenylamine corresponding to the amine component; the yield of the acid component of the Naphthol is variable, and better yields of the acid are obtained by hydrolysis of the *N*-cyanuryl derivative (XIV). When (XIV) is treated with dimethylamine, the two reactive chlorine atoms are replaced and the product (XV) then undergoes very smooth hydrolysis to the acid and the triazine derivative (XVI). Thus it has been shown that the constitution of Naphtol AS-KG is (XVII)[5].

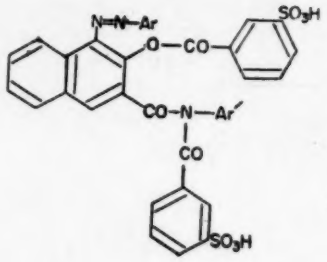


Dinitrochlorobenzene attacks the reactive methylene group in acetoacetaniliide on heating an ethanolic solution containing a molar proportion of sodium hydroxide; under these conditions the acetyl group is split off and the product is 2,4-dinitrophenyl-acetanilide (XVIII). Similarly Naphtol AS-IRG (XIX) yields (XX)[5].

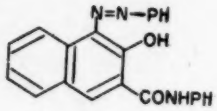


The Neocotone dyes of Ciba have been withdrawn from the commercial range and do not find a place in the new Colour Index; but their chemical constitution is of interest. They have been stated in the literature to be of the type (XXI), prepared by condensing a pre-formed azoic dye (XXII) with *m*-sulphobenzoyl chloride[16], but this needs confirma-

tion since the hydroxyl group in 1-benzeneazo-2-hydroxy-3-naphthanilide (XXII) is likely to be unreactive.



(XXI)

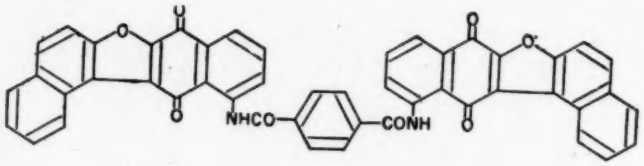


(XXII)

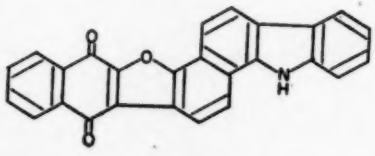
Vat Dyes

Patent activity on indigoids has almost ceased; in the anthraquinone field there are only minor structural variations of the established types. This area, however, offers numerous problems for research on constitution, reaction mechanism, steric effects, light absorption, and photochemical activity in the degradation of cellulose. Considering the technical importance of the vat dyes, fundamental work on these problems has been very limited[17].

Vat dyes not derived from anthraquinone or benzanthrone can be prepared from 2,3-dichloro-1,4-naphthoquinone[18] and some dyes of this type appear to have technical possibilities[19,20]. Examples are the bright orange dye (XXIII) and the red-brown to violet dyes (XXIV) in which the ring system carries nitro, amino, and other substituents.



(XXIII)



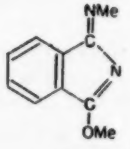
(XXIV)

Phthalocyanines

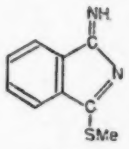
Because of the brightness and stability of the phthalocyanine pigments, attempts have been made for many years to apply them to textiles. Partly sulphonated cobalt phthalocyanine behaves as a vat dye and has been marketed (Indanthrene Brilliant Blue 4G), but the chlorine fastness is poor. The mechanism of the reduction and re-oxidation of cobalt

phthalocyanine has not yet been elucidated. When phthalocyanines are treated in methanol with oxidizing agents such as butyl hypochlorite, chlorine, bromine or dibenzoyl peroxide, the red-brown products are soluble in solvents such as ethylene glycol monomethyl ether, and the solutions may be used for padding cotton, the original phthalocyanine being regenerated by treatment with a reducing agent such as sodium bisulphite or hydrosulphite. Solvent-soluble products of copper and nickel phthalocyanines resulting from reversible oxidation can also be obtained by treating metal-free phthalocyanines with a halogen in an alocholic solution of a salt of copper or nickel[21].

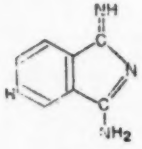
By suitable reactions on phthalonitrile or phthalimide or their derivatives, iso-indolenines can be isolated as intermediates in phthalocyanine synthesis; iso-indolenines such as (XXV), (XXVI) and (XXVII; R=H or Ph) (Phthalogens, Bayer) can be printed on textile fabrics together with a copper salt, and under mild conditions of heating or steaming the metal phthalocyanine is formed on the fibre as a brilliant pigment with excellent fastness properties[22,23].



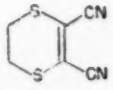
(XXV)



(XXVI)



(XXVII)



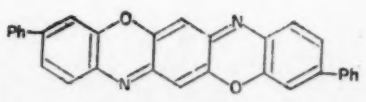
(XXVIII)

The action of dimercaptomaleic acid dinitrile on ethylene dihalogenides yields 1,2-dicyano-3,6-dithiacyclohexene (XXVIII), which is useful for the preparation of pure and mixed phthalocyanines, thus expanding the colour scale of the phthalocyanines to violet, dark blue and black[24].

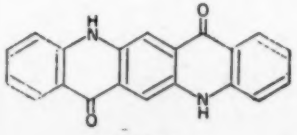
A clear yellowish green azoic dye has now become available, although the Naphthol has the disadvantage that it has no affinity for cellulose fibres and can only be applied to cotton by padding or Rapidogen printing. Fast green shades are produced from Naphtol AS-FGGR, which is copper phthalocyanine to which four pyrazolone rings have been linked by chromophore-insulating groups (such as CONH)[23].

Pigments

The triphenodioxazine (XXIX) is a reddish violet pigment with high light-fastness and tinctorial value, disclosed in a patent some years ago, but it found little use commercially because of its very severe flocculation in paint systems. An important advance is the application of this pigment (or its chloro or bromo derivative) after treating it with the aluminium salt of the pigment substituted by carboxyl or sulphonic groups; the treated pigments are not altered tinctorially, but exhibit excellent resistance to flocculation in paint systems[25].



(XXIX)



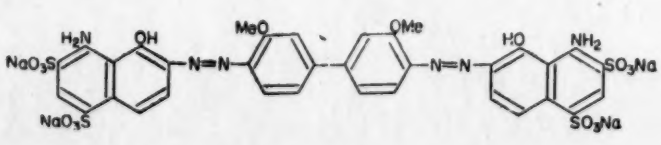
(XXX)

Quinacridones (XXX; 5, 14-7, 12-tetrahydro-5, 12-diazapentacene-7, 14-dione), carrying halogen, alkyl or alkoxy substituents, are brilliant orange to violet pigments of high fastness and durability. The linear quinacridones can be obtained in three crystal phases, α, β, and γ with distinctive shade and pigment properties.

Mechanism of Dyeing Cellulose

Theories of dyeing, so far at least as cellulose fibres are concerned, keep going round in a circle[27]. The tendency of a fibre to adsorb a dye from aqueous solution and to retain it, which is the basis of normal dyeing processes, is sometimes termed "substantivity." In his book[28] on the physical chemistry of dyeing Vickerstaff has ably expounded the thermodynamic approach to dyeing, defining the affinity of a dye for a fibre as the difference in the standard chemical potential of the dye in the fibre phase and the solution phase. He therefore measures substantivity in terms of the change in free energy accompanying the adsorption of the dye, and he has developed equations for evaluating substantivity. Wegmann[29] rejects this concept of substantivity; Wirz and Zollinger[30] in their recent work on the substantivity of polyene dicarboxylic acids and quaternary ammonium salts derived from benzidine have limited themselves to the determination of "relative substantivity" as the ratio of dye on the fibre to dye in solution after equilibrium has been attained. The greater the shift in equilibrium in favour of the adsorbed dye, the greater the degree of substantivity. Their conclusion that the substantivity of these compounds is mainly or exclusively due to van der Waals forces is valid, but as Zollinger himself has stated[31] these experiments do not prove that no hydrogen bonding to cellulose takes place in direct dyes[32]. It has to be recognized that no simple generalization can cover all dyeing mechanisms. Dyeing processes depend on the operation of one or more of three forces: van der Waals forces (electronic dispersion forces), hydrogen bonds, and electrostatic forces. If we consider a dye whose structure permits hydrogen bonding as well as van der Waals and coulombic attractions, no methods are yet available by which these can be separately determined.

Another aspect of the substantivity of dyes to cellulose, which needs much more investigation and about which some misconceptions persist, is the need for planarity and for the spacing of groups in a dye molecule at certain distances to enable hydrogen bonding to take place. Because of the large number of hydroxyl groups in cellulose and the flexibility of the cellulose chain, it is necessary to repeat the point made elsewhere that all substantive dyes need not be "long, linear and planar molecules" as stated so frequently. Considerable deviations in both these factors of planarity and spacing of hydrogen-bonding groups are permissible, and several examples of dyes illustrating this view have been cited[33]. The possibilities of hydrogen bonding and the complexity of the whole problem of cellulose-dye interaction are shown by the formula of a simple and well-known direct cotton dye, Diamine Sky Blue FF.



Diamiane Sky Blue FF

The Dyestuff Industry in India

In a volume dedicated to the memory of Acharya Prafulla Chandra Ray, the pioneer of the Indian chemical industry, it is appropriate to record the rapid expansion of the dyestuff industry in India. The list of dye and pigment manufacturers in the new Colour Index includes several Indian firms. Although the industry is at present largely based on imported intermediates, there is reason to hope that all the basic intermediates will be manufactured and that a self-contained industry, which will fully meet our requirements of dyes and related organic chemicals, will be established in the course of the next few years.

One aspect of the manufacture of organic intermediates and dyes on which the attention of Indian manufacturers, especially those operating on a small scale and with inadequate resources, needs to be focussed is the increasing consciousness in other countries of chemical caracinogenesis and other health hazards. The use of β-naphthylamine, the most active carcinogen among dye intermediates, is being eliminated, and attempts are being made to synthesize β-naphthylamine derivatives, such as Naphtol AS-SW and Indanthrene Red RK, from 2-naphthylamine-1-sulphonic acid (Tobias acid)[34] or by other routes. Arsenic pentoxide is used in halogenations and aminations, but procedures by which it can be avoided are being sought. Health hazards in handling chemicals are considerably increased under hot and humid conditions. Benzanthrone, for instance, appears to present no special problem elsewhere, but photochemical toxicity has been observed in India. Stringent precautions should be enforced in dyestuff factories, and a programme of research on the physiological action of the largely used organic intermediates under Indian conditions should be undertaken.

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Catalytic Vapour Phase Oxidation of Organic Compounds in the Fixed as well as in Fluidized Beds

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Oxidation plays an important role in the organic chemical industry. The controlled catalytic oxidation of hydrocarbons or other organic compounds to obtain commercially important intermediate oxidation products, is the most promising field and has great utility in petro-chemical as well as coal-chemical industries. Among the more important chemicals, which are products of oxidation, may be mentioned phthalic anhydride, ethylene oxide, adipic acid, acrolein, and various other oxygenated organic compounds.

Since there is generally a scope for improvements in conversions and reduction in cost, research and development efforts are being constantly pursued in this segment of the chemical process industry. With this in view, the catalytic oxidation of ethylene, benzene, crotonaldehyde and *o*-, *m*- and *p*-xylenes, etc. was exhaustively studied by Bhattacharyya and his coworkers. The results obtained in their earlier investigations have already been reported.

In the present article, the important contributions made by Bhattacharyya and his school in this field during the last few years have been briefly reviewed and the results of their recent and unpublished work, specially those in the fluidized bed operations, have been incorporated. The work of other eminent researchers have also been referred to in course of the discussion.

Oxidation of Ethylene to Ethylene Oxide

The catalytic oxidation of ethylene to ethylene oxide, employing a static bed of catalyst, has been the subject of a number of patents and a few papers. The catalyst generally employed consists of silver oxide deposited on metallic or non-metallic supports. The only earlier and significant published work on the oxidation of ethylene seems to be that of McBee *et al.*[1] who employed synthetic corundum as the carrier. A conversion of 30% (on the basis of ethylene fed) and a selectivity of 45% for ethylene oxide were reported at a space velocity of 1,500 with an air-ethylene ratio of 17.5 .

Bhattacharyya and his coworkers made a systematic and exhaustive study on this reaction in a flow reactor using fixed catalyst beds employing a large number of catalyst compositions. For experimental procedure and elaborate discussion reference may be made of previous publications of Bhattacharyya *et al*[2].

The catalytic oxidation of ethylene was systematically investigated from manifold aspects, viz., the suitability of different oxidising catalysts, effect of catalyst supports, promoter action of different elements, etc. Preliminary studies indicated that the oxida-

tion proceeded specifically on the silver oxide catalyst; the other catalysts used were either inactive or led to complete oxidation to carbon dioxide and water. With a view to securing high conversions to ethylene oxide, the effect of a number of substances as promoters for silver oxide catalyst was studied. These studies indicated that such substances might be broadly classified as follows:

(*i*) Substances indifferent in nature, bringing about little or no change in activity of silver oxide, e.g., oxides of tin and zinc.

(*ii*) Substances which lead to an enhancement in activity of silver oxide catalyst without causing a marked fall in selectivity, e.g., compounds containing lithium, copper, calcium, strontium, barium, and magnesium.

(*iii*) Substances extremely degradative in nature, e.g., oxides of mercury, iron or manganese.

(*iv*) Substances causing partial or total loss in activity of silver oxide, e.g., compounds containing sodium, potassium, lead, or chlorides.

As a catalyst support, quartz was found superior to pumice, kieselguhr, activated alumina, alumina gel, silica gel, etc. The activity of the catalyst was partially lost on incorporation of sodium, while potassium completely poisoned the catalyst. The promoter action of the alkaline earth elements was in the order: Mg > Ba > Ca > Sr. The activity of the silver oxide-quartz catalyst was considerably enhanced by the addition of small amounts of barium peroxide. The fresh catalyst thus obtained gave a conversion of 39.7% ethylene to ethylene oxide with a selectivity of 62.6% at 290°, space velocity of 1500 c.c./hr.c.c. and air/ethylene ratio of 9. The value was as high as 38.6% conversion and 63.8% selectivity after a use of 70 hours. A higher activity was shown by a catalyst promoted by magnesium oxide. Conversion of about 43% with a selectivity of 64% was obtained per single pass at 280° with the same space velocity and air/ethylene ratio as above. The activity of the magnesium oxide promoted catalyst was, however, found to decrease after a use of 70 hours and the reaction temperature thereafter had to be increased to secure the same conversion as the fresh catalyst. The effect of temperature on the activity of the best catalyst, that is, Ag_2O-BaO_2-quartz (31.39:1.84:100) is shown in Fig. 1.

In order to elucidate the mode of action of various catalysts, decomposition of ethylene oxide was studied on some representative catalysts and supports at various temperatures. These studies indicated that the degradative action of iron, manganese, etc. was due to their promotion of instability of ethylene oxide.

With a view to ascertaining the optimum conditions for obtaining maximum yield of ethylene oxide from ethylene in presence of silver-based catalysts, the effects of a number of reaction variables, viz., catalyst concentration, method of preparation of catalyst, time of contact, etc., were studied. These studies indicated that a concentration of 32.39 g. of silver oxide on 100 g. of purified quartz was the optimum for oxidation reaction. The effect of a number of promoters indicated that barium oxide and magnesium oxide were efficient promoters for the silver oxide catalysts.

The presence of water vapour in concentrations beyond 0.4% (by volume) in the inlet gas lowered the efficiency of the oxidation. The fall in activity was independent of the concentration of the water vapour for values between 1 and 5% of the inlet gas. It was found that the catalyst, which had undergone partial inactivation on prolonged use, was completely restored to the state of its original activity by treatment with a gas mixture containing ethylene, air, and small amounts of water vapour.

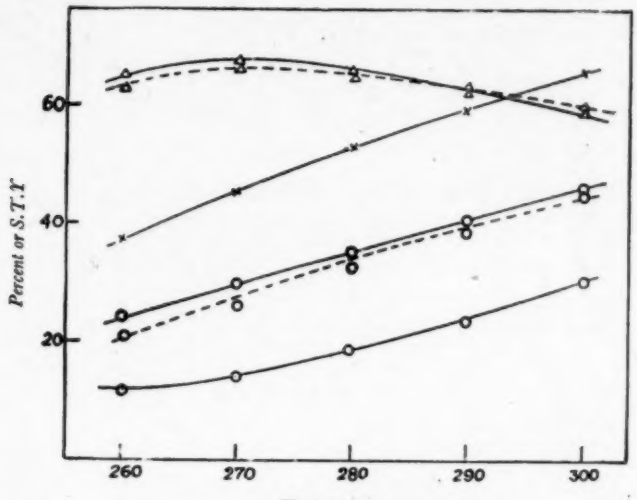


FIG. 1. Effect of temperature on the activity of silver oxide-barium oxide-quartz catalyst.

S.V.≈1530 Air/C_2H_4≈92
Fresh Catalyst Used Catalyst
Conversion to C_2H_4O
Conversion to CO_2
×: S.T.Y. Δ : Selectivity.

Marked loss in the efficiency of the oxidation was found to result when ethylene, prepared from ethanol was used without any elaborate purification to remove impurities like butadiene, carbon dioxide, and possibly small amounts of ether. The time of contact of the gas with the catalyst (space velocity) had a pronounced effect on the efficiency of the oxidation. While the conversions to ethylene oxide and carbon dioxide decreased with increasing space velocity, the space-time-yield of ethylene oxide registered a progressive rise under these conditions. The efficiency of the oxidation also depended on the concentration of ethylene in the gas mixture; with decreasing concentrations, the space-time-yield of ethylene oxide progressively decreased.

The activity of the catalyst also depended on its method of preparation. The catalyst, prepared by coprecipitating barium and silver carbonates from a mixture of barium and silver nitrate solutions and subsequently reducing the carbonate mixture, was found to be less active than the catalyst, prepared by mixing silver oxide with barium peroxide mechanically. The barium oxide-promoted catalyst, prepared by using silver oxide precipitated at 60°, had higher optimum activity than the catalysts containing silver oxide precipitated at 0° or 100°.

Very recently Twigg[3] has studied the kinetics of this reaction in a flow reactor using a silver catalyst. The mechanism suggested by him and supported by Murray[4] involves the chemisorption of oxygen atoms on the catalyst surface followed by the reaction of gaseous or weakly adsorbed ethylene molecules either with one oxygen atom to form ethylene oxide or with two atoms to form products (like CH_3CHO) that are rapidly oxidised to CO_2. Murray later found that the oxidation of ethylene to ethylene oxide involved an activation energy of 12 K cals., whereas the corresponding reaction to CO_2 had an activation energy of 15 K cals.

Recently Andrianova and Todes[5] have put forward the following kinetic equation for the range of conditions investigated by them.

$$\frac{-d\ (C_2H_4)}{dt} = 100e^{\frac{13{,}000}{RT}} \times (u)^{\frac{1}{2}}[O_2]^{\frac{1}{2}}$$

where u = volumetric gas flow rate.

Orzechowski and MacCormack[6] from their elaborate studies on the kinetics of ethylene oxidation with Ag-catalyst have suggested the following scheme:

$$\begin{array}{ccc} C_2H_4 + O\text{-}Ag & & C_2H_4 + O\text{-}Ag \\ \uparrow\downarrow & & \uparrow\downarrow \\ C_2H_4\text{-}O\text{-}Ag & & y\text{-}Ag \\ \uparrow\downarrow & & \uparrow\downarrow \\ C_2H_4O + Ag & & y + Ag \end{array}$$

Where y is isomeric with ethylene oxide (i.e. CH_3CHO, $CH_2{=}CHOH$ etc.) and is very rapidly oxidised to CO_2 and H_2O.

It has recently been reported that in some factories the oxidation of ethylene to ethylene oxide is also carried out in the fluidized catalyst bed, but all their findings are carefully guarded by patents.

The present authors have undertaken this problem of oxidation of ethylene to ethylene oxide in the fluidized catalyst bed and the work is in progress.

Oxidation of Benzene to Maleic Acid

Maleic acid, in view of its highly reactive nature and of the reactivity of its anhydride and amide, finds numerous applications in chemical industry. Of the many hydrocarbons, open chained or ringed, benzene seems to be the most profitable choice as the starting material for maleic acid.

A considerable amount of work has been done on the vapour phase catalytic oxidation of benzene. Special mention may be made of the contributions due to Weiss and Downs[7]. But the results of most of these investigations are covered by patents and very little is disclosed concerning the method of approach to the problem, the nature of the catalysts employed, and the details of experimental conditions or the results obtained.

A survey of the published work on the oxidation of benzene in the vapour phase shows that the maximum conversion by maleic acid is about 57% on the weight of benzene used, per single pass. The catalyst employed was V_2O_5–MoO_3 (70:30)-pumice, promoted with 5% Co_2O_3. But much higher conversions are disclosed in the patent literature. It was therefore considered worthwhile to try to raise the efficiency of the process by judicious selection of catalysts.

Bhattacharyya and Venkataraman[8] studied the oxidation of benzene with a large number of catalyst compositions (single, binary, promoted, unpromoted, supported, and unsupported) under a wide range of operating conditions. Their observations have already been reported. The salient points of their findings will be discussed here.

Previous studies on the oxidation of benzene to maleic acid have been carried out mainly with catalysts supported on substances like pumice, asbestos, or metallic aluminium. Preliminary experiments showed, however, that kieselguhr was the most promising catalyst support.

A systematic study was therefore undertaken and forty different catalyst compositions were tried, of which the following catalyst systems were found to be quite active:

(1) V_2O_5 — kieselguhr (51.84: 100)
(2) MoO_3— kieselguhr (48.72:100)
(3) WO_3 — kieselguhr (50.17:100)
(4) V_2O_5: MoO_3 : kieselguhr (38.9 : 16.64:100)
(5) V_2O_5 : WO_3 : kieselguhr (38.9 : 4.32 : 100)
(6) V_2O_5 : WO_3 : kieselguhr (38.9 : 16.64 : 100)
(7) V_2O_5 : UO_3 : kieselguhr (38.9 : 4.32 : 100)
(8) V_2O_5 : UO_3 : kieselguhr (38.9 : 16.64 : 100)

The comparative activity of the above single and binary catalyst systems are summarised here.

Catalyst (I) was found to be more efficient than the pumice or asbestos-supported catalysts described by earlier workers. More than 27% conversion to maleic acid was possible with this catalyst in a contact time of 0.2 sec.

Catalysts (2) and (3) had poor activity. Catalyst (4) was very active and had the additional advantage of being fairly efficient over a wide range of space velocity. Thus, the conversion to maleic acid was 57% at 2618 l./h./l., and 51% at 11000 l./h./l. Consequently, maximum S. T. Y. was considerably higher than in the case of catalyst (1). Catalysts (5-8) were more active under some experimental conditions than catalyst (1), but were less active than catalyst (4).

Kieselguhr, pumice, asbestos, silica gel, etc. were tried as catalyst support. Of these kieselguhr was found to be the best.

It was further observed that the activity of the V_2O_5-MoO_3-kieselguhr catalysts depended on the ratio of V_2O_5/MoO_3, the optimum being 1 to 2.3. The optimum total oxide ($V_2O_5 + MoO_3 + Co_2O_3$) of the kieselguhr supported catalysts was found to be 22%.

Various oxides like Co_2O_3, WO_3, UO_3, ZrO_2, TiO_2, etc. were incorporated with V_2O_5—MoO_3-kieselguhr catalyst to investigate their promoting activity. Co_2O_3 was found to be the best promoter. Addition of 2% cobalt oxide to vanadium pentoxide-molybdenum trioxide-kieselguhr catalyst was almost totally ineffective, but the catalyst with nearly 3% of cobalt oxide (on the basis of the total weight of the supported catalyst) was very active. With this catalyst (9) (V_2O_5-MoO_3-Co_2O_3-kieselguhr) though the maximum conversion was 57%, as in the case of unpromoted catalyst, the maximum S. T. Y. was considerably higher, the conversion being almost constant for a wide range of space velocity (2500 to 11000 l./h./l.). Further additions of cobalt oxide reduced the activity.

Various methods of preparation of V_2O_5-MoO_3-kieselguhr were adopted to find out the effect of method of preparation on the catalytic activity. It was observed that the catalyst prepared by thermal decomposition of oxalate salts was the most active. With this catalyst a maximum conversion of 57% was obtained. The catalyst prepared by this method was also found to retain its activity for a longer time.

Bhattacharyya and Venkataraman[8] measured the surface area of different catalyst

samples by B. E. T. method to find out a definite relation between catalytic activity and surface area; but no such correlation was achieved (Table I).

TABLE I

Surface area and catalytic activity.

Catalyst No. or support.		Surface area ($m^2/g.$).	Max.S.T.Y. (maleic acid), (g./h./l.).	
1 (V_2O_5)	..	23.51	79.7	
2 (MoO_3)	..	11.38	2.8	Influence
4 (V_2O_5-MoO_3)	..	16.09	220.1	of catalyst
9 (V_2O_5-MoO_3-Co_2O_3)	..	10.72	229.1	composition.
36 (6.8% oxides)	..	20.41	65.5	
37 (12.8% oxides)	..	12.54	107.6	Influence of
38 (22.6% oxides)	..	11.42	226.0	catalyst
9 (36.9% oxides)	..	10.72	229.1	concentration
39 (46.7% oxides)	..	10.42	225.9	
40 (53.8% oxides)	..	10.24	222.9	
35 (ammonium salt method)	..	10.34	145.6	Influence of method
4 (oxalic acid method)	..	16.09	220.1	of preparation
9 (kieselguhr)	..	10.72	229.1	
26 (pumice)	..	3.16	159.2	
27 (kaolin)	..	11·57	209.7	Influence of nature
28 (silica gel)	..	320.3	Nil	of support
33 (ignited kieselguhr)	..	8.38	197.0	
34 (B.D.H. kieselgurh)	..	..	149.7	
Purified Indian kieselgurh	..	30.44	..	
Purified (ignited, 400 for 4 h.)	..	23.97	..	
B.D.H. kieselguhr (flux calcined)	..	1.44	..	Surface area data on
B.D.H. pumice, purified	..	1.31	..	supports
Silica gel	..	383.10	..	

A calculation of the extent of chemisorption of oxygen on these catalysts in relation to surface areas showed that only 0.8% of surface was active in catalyst (1), assuming monolayer chemisorption. The respective values in catalysts (4) and (9) were 9.7% and 13.4%. When compared on the basis of adsorption per unit area of the surface, the amounts of oxygen adsorbed were uniformly higher in the case of more active catalysts.

The differential heats of adsorption, Q, were calculated according to the equation:

$$\log p_1 - \log p_2 = \frac{Q}{4.58}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

where p_1 and p_2 were the pressures required to give the same amount of adsorption at temperatures T_1 and T_2 respectively. In the temperature interval of the declining isobar (500-540°), there was a definite indication of the existence of activated adsorption. The differential heat of adsorption on 6.5. g. of catalyst (4) was found to be 36,840 cal./mole at 1.3 c.c. (S.T.P.) adsorption and 12,740 cal./mole at 1.8 c.c. adsorption. For the more

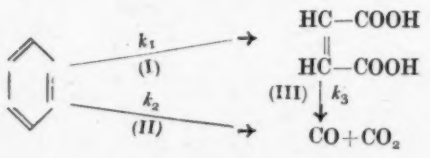
active catalyst (9) the corresponding values were 34,340 cal./mole and 14,870 cal./mole. Taylor *et al.*[9] reported similar results for the adsorption of hydrogen on platinum catalysts.

The value of activation energy, E, according to the equation

$$\log t_1 - \log t_2 = \frac{E}{4.58}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

where t_1 and t_2 are the time periods needed to complete adsorption of a specified amount of gas at temperatures T_1 and T_2 respectively, was constant for catalyst (9) at approximately 41 kcal. /mole for adsorption of 0.55-1.10 c.c. (S.T.P.) of oxygen at 480-500°, and was less than the 51 kcal./mole required for adsorption of 1.10 c.c. of oxygen by the less active catalyst (4) in the same temperature range. In the latter case the value of E decreased, however, with the extent of adsorption and was only 37 kcal./mole at 0.65 c.c. adsorption; it was also greatly dependent on the temperature range studied, being nearly 65 kcal./mole at 420-60° and 32 kcal./mole at 460-80° for 0.65 c.c. adsorption. The value of 46 kcal./mole at 460-500° for 1.0 c.c. adsorption on catalyst (4) and the value of 41 kcal./mole for catalyst (9) compared well with the value of 45 kcal./mole observed by Cameraon *et al.*[10] who carried out a study of the exchange of isotopic oxygen between vanadium pentoxide and oxygen. Bhattacharyya *et al.*[2] concluded from their investigations that the high values for activation energy suggested that the process involved either the dissociation of oxygen molecules on the surface of the solid or the loosening of the vanadium-oxygen bonds in vanadium pentoxide.

It has been established quite recently by a number of workers that principal overall reactions can be represented by the following scheme:



The reaction step (I) is supposed to proceed through several consecutive reactions as given below:

Benzene → Phenol → Quinone → Maleic acid

Hammar *et al.*[11] from their studies on the kinetics of the oxidation of benzene with various catalysts observed that the ratio k_2/k_1-k_3 was near about 0.25. They calculated the activation energies of the three reactions and found them to be lying within a range of 28±4 k-cal./mole. Holsen[12] put forward a general rate equation as follows:

$$\frac{[MA]}{\Theta_0} = \frac{k_1}{k_3 - (k_2 - k_1)} \times \left(e^{-(k_1 - k_2)t} - e^{-k_3 t}\right)$$

where k_1 = first order rate constant for reaction (I)
k_2 = " " " " " " (II)
k_3 = " " " " " " (III)
Θ_0 = initial benzene concentration
[MA] = concentration of maleic acid.

The oxidation of benzene in the fluidized catalyst bed has been reported recently by Thampy *et al.*[3], but the results reported by them do not seem to be very promising. The present authors have of late started this work.

(*a*) *Oxidation of* o-, m- *&* p-*Xylenes in the Fixed Catalyst Bed*

(i) o-*Xylene Oxidation.*—Phthalic anhydride, a product of the oxidation of *o*-xylene, is mainly employed in the manufacture of dyes, alkyd resins and plasticizers, and also in other fields. The other source of phthalic anhydride is naphthalene. But for reasons more than one, *o*-xylene seems to be a more promising source of phthalic anhydride.

Park and Allard[14] studied the oxidation of a crude mixture of xylenes (*o*-, *m*- and *p*-) over a few catalysts (oxides of Zr, Mo, W, etc.) in a flow reactor and reported their results as the total acid and total aldehyde produced. The maximum conversion to total acid was only 18.2%, although yields based on converted xylenes were in the 50 to 60% range. V_2O_5 was found to be the most active catalyst and the optimum temperature range was 450-530°. But from their data, it is not possible to ascertain as to what extent each of these xylenes is oxidised and what the product distributions with different catalysts are. For experimental procedure and a thorough discussion of the results of the oxidation of xylenes, reference may be made to previous publications of Bhattacharyya *et al*[15].

The data on the efficiency of twenty different catalysts, presented in Table II, show that the catalysts containing V_2O_5 are the most efficient. The action of various promoters on V_2O_5 catalysts was also studied.

TABLE II

Comparative activity of different catalysts.

No.	Catalyst.	Space velocity (c.c./hr./c.c.)	Molar air/xylene ratio	Temp. Bath.	Temp. Bed.	Conversion% (anhydride). Phthalic.	Conversion% (anhydride). Maleic.	Selectivity.	Space-time yield. (g./hr./l.
1	MoO_3-Kieselguhr (32.6:100)	6180	335	400	420	9.3	6.7	58.1%	11.4
2	V_2O_5-kieselguhr (31.1:100)	6180	360	360	440	42.7	11.3	79.1	51.3
		3910	230	360	480	36.9	13.3	73.4	42.0
		7110	230	360	500	40.0	14.8	72.9	78.4
		6722	171	360	520	37.0	15.2	71.0	95.7
3	Sn $(VO_3)_4$	4240	230	330	410	14.5	5.5	72.5	17.8
4	$AgVO_3$	6180	360	320	380	12.4	5.3	70.1	12.1
5	$Cu(VO_3)_2$-kieselguhr (34:100)	No acid formation at any temperature between 240° and 340°.							
6	Phosphomolybdic acid-kieselguhr (31:100)	4050	210	400	425	6.2	10.8	36.4	8.2
7	V_2O_5-silica gel (20:100)	4290	220	420	465	15.4	14.2	52.2	20.2
		6180	320	400	430	10.0	13.5	42.9	12.8
8	V_2O_5-kieselguhr (51.8:100)	6180	360	360	420	42.4	12.5	77.2	50.4
9	V_2O_5-MoO_3-kieselguhr	4770	155	350	430	36.6	12.6	74.4	71.8
		7150	205	360	450	36.0	11.6	75.7	78.5
		3460	357	350	400	39.5	11.0	78.1	25.2
10	V_2O_5-Co_2O_3-kieselguhr (31.1:1.4:100)	4290	210	340	440	31.8	14.1	69.3	41.8
		4290	515	360	400	25.3	9.6	72.6	13.9
		5720	280	360	440	31.0	15.1	67.3	41.6

TABLE II (contd.)

No.	Catalyst.	Space velocity (c.c/hr./c.c.)	Molar air/xylene ratio.	Temp. Bath.	Temp. Bed.	Conversion% (anhydride) Phthalic	Conversion% (anhydride) Maleic	Selectivity.	Space-time yield (g./hr./l.)
11	V_2O_5-UO_2-kieselguhr	4290	220	360	450	30.5	16.4	65.0%	38.6
	(31.1:4.6:100)	7145	367	360	430	36.8	12.5	74.7	47.3
12	V_2O_5-cerium oxide-kieselguhr (31.1:2.9:100)	4290	222	340	460	8.9	5.5	61.8	10.9
13	V_2O_5-Co_2O_3-MoO_3-kieselguhr	6190	365	380	450	39.0	14.8	72.5	42.8
	(19.5:1.3:7.7:100)	8110	206	370	520	37.8	13.7	73.5	98.5
14	Fused V_2O_5	5740	363	460	465	59.0	9.1	86.7	61.4
		5740	275	460	490	61.7	9.6	86.6	85.6
		5740	685	460	475	56.3	7.9	87.8	31.1
15	Fused V_2O_5-Co_2O_3	5760	290	460	500	55.2	15.5	78.1	72.2
16	Fused V_2O_5-K_2SO_4 (100:26)	5760	275	470	510	46.0	9.3	83.2	66.1
17	Fused V_2O_5-kieselguhr (31:1:100)	5760	285	450	510	39.0	10.4	78.9	53.2
18	Fused V_2O_5-pumice(162:100)	5760	410	480	500	46.9	9.5	83.5	42.0
19	Fused V_2O_5-pumice (243:100)	5760	383	480	510	51.8	9.3	84.8	51.4
20	Fused V_2O_5-silica gel (229:100)	5760	290	480	500	48.4	9.4	83.8	63.5

With catalyst (9) the maximum conversion was only 36.6% at 430°. Catalyst (10) was more degradative than (9), maximum conversion being 31.8% at 440°.

The use of UO_2 with V_2O_5 catalyst resulted in a catalyst which was sensitive to heat. At 450° the catalyst showed a conversion of 30.5% to phthalic anhydride. But beyond this temperature there was a sharp fall.

V_2O_5-CeO_2-kieselguhr catalyst gave a very poor conversion to phthalic anhydride, the maximum value recorded being 8.9% at 460°.

The double promoted catalyst V_2O_5-MoO_3-Co_2O_3-kieselguhr exhibited maximum activity at 450°. At this temperature conversion to phthalic anydride was 39.0%.

Several fused V_2O_5 catalysts were also studied. Fused V_2O_5 did not show any reaction from 320° to 440°. The reaction slowly started at 450° and the catalyst became very active at 460°. At 490° a conversion of 61.7% to phthalic anhydride was obtained.

Incorporation of cobalt oxide in the V_2O_5 made the fused catalyst quite degradative. The activity of this catalyst at 500° was about 5.6% less than that of the unpromoted catalysts.

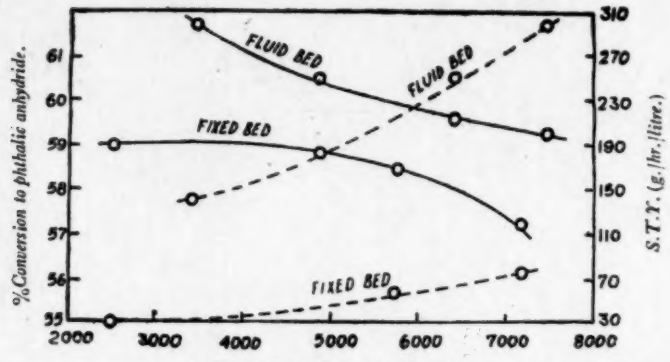
Fused V_2O_5-K_2SO_4 catalyst was also found to be active only at 450° or more. The conversion to phthalic anhydride was, however, much less, e.g. at 510° it was only 46.03%

Of the number of supports like kieselguhr, pumice, silica gel, etc., pumice was found to be the best.

The process yield with V_2O_5-pumice (243:100) was 51.8%, whereas the space-time yield was 84.8 g./hr./litre.

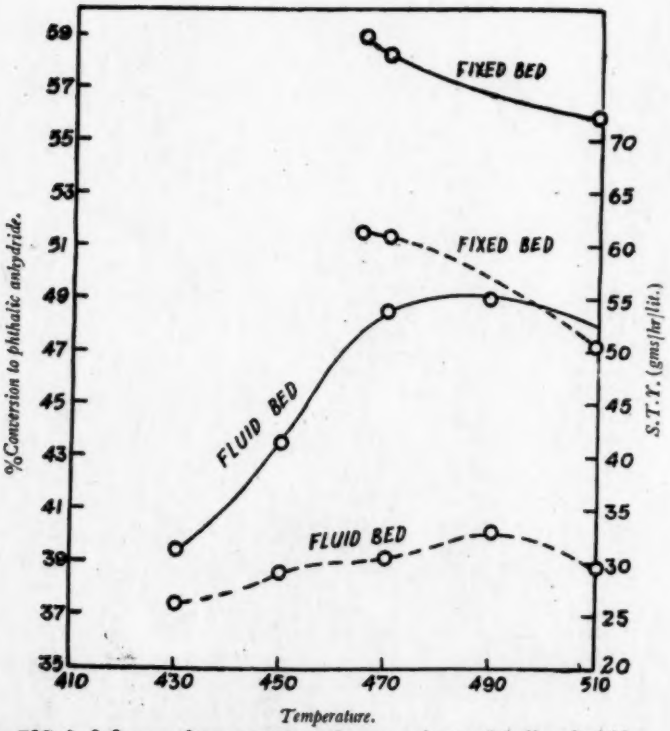
Use of oxygen instead of air for the oxidation did not in any way affect the conversion to either phthalic anhydride or maleic anhydride.

The effects of space velocity, temperature, air/xylene ratio on the yield of phthalic anhydride are shown in Figs. 2-4.



Space velocty (lit/hr/lit. of cat.)

FIG. 2. Influence of space velocity on the conversion to phthalic anhydride.
— — — — — — — S.T.Y.
———————% Conversion



Temperature.

FIG. 3. Influence of temperature on the conversion to phthalic anhydride.
— — — — — — — S.T.Y.
———————% Conversion.

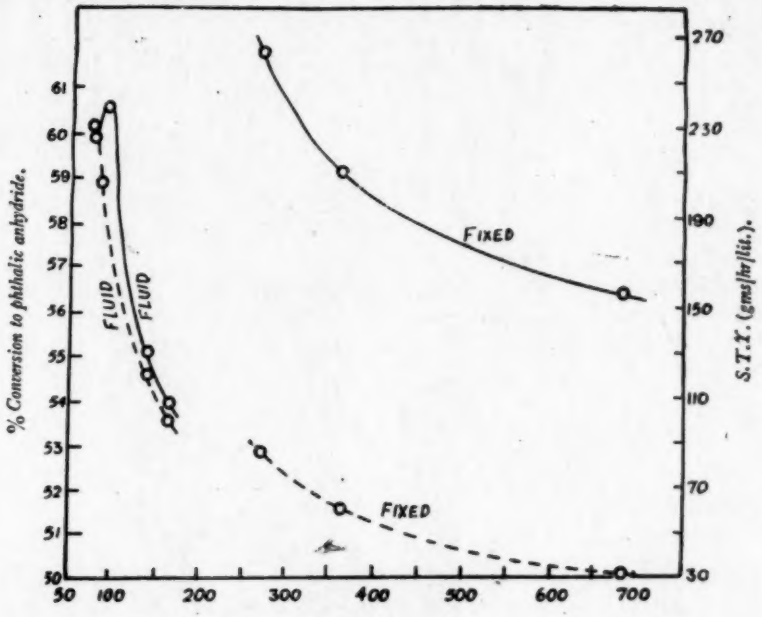


FIG. 4. Influence of air/xylene ratio on the conversion to phthalic anhydride.
— — — — — — — S.T.Y.
——————— % Conversion

(*ii*) p-*Xylene Oxidation*.—The chief product of oxidation of *p*-xylene is terephthalic acid, which is extensively used for making synthetic fibres like 'Terylene', and 'Dacron'. The following catalysts were studied for the oxidation of *p*-xylene:

(1) V_2O_5—kieselguhr

(2) V_2O_5-MoO_3—kieselguhr

(3) V_2O_5—MoO_3—Co_2O_3—kieselguhr

(4) $Sn(VO_3)_4$

(5) $AgVO_3$

(6) Fused V_2O_5

Catalyst (1) was sufficiently active at 480°, the conversion to *p*-toluic acid was only 1.0% and to terephthalic acid 0.6%, whereas 21.0% of *p*-xylene passed was converted into maleic anhydride. Temperature increase only augmented the formation of maleic anhydride and *p*-tolualdehyde.

The two promoted catalysts, V_2O_5-MoO_3-kieselguhr and V_2O_5-MoO_3-Co_2O_3-kieselguhr, showed a behaviour analogous to the unpromoted catalyst.

In the case of tin vanadate and silver vanadate catalysts, the overall activity of the catalysts was very poor.

The fused V_2O_5 increased the conversion to maleic anhydride, *p*-tolualdehyde, and quinone to an appreciable extent, though the yields of terephthalic acid and *p*-toluic acid did not increase much. For example, at 540° a conversion of 1.1% of *p*-xylene to terephthalic acid, 2.1% to *p*-toluic acid, and 32.3% to maleic anhydride was received at a space-velocity of 5765 c.c./hr./c.c. The vapour phase catalytic oxidation process, which produces such high yields of phthalic anhydride in the case of *o*-xylene oxidation, does not seem to be feasible for the production of terephthalic acid from *p*-xylene.

(*iii*) m-*Xylene Oxidation*.—The data available on the oxidation of *m*-xylene are extremely meagre. In both the patented and published literatures, mention is made only of laboratory synthesis of isophthalic acid using some of the common oxidising agents, such as $KMnO_4$, $K_2Cr_2O_7$, etc.

The following catalysts were used for the study of oxidation of *m*-xylene:

(1) V_2O_5 (31.1: 100)

(2) V_2O_5–MoO_3-Co_2O_3 -kieselguhr (19.2:7.7:1.3:100)

(3) Fused V_2O_5

In the reaction products isophthalic acid, *m*-tolualdehyde, and maleic anhydride were found to be present. No *m*-toluic acid could be detected.

Using catalyst (1) 1.1% conversion to isophthalic acid and 21.3% to maleic anhydride were obtained. With catalyst (2) the conversion to maleic anhydride was greater (22.3%), but the oxidation of other products, *i.e.*, aldehyde, quinone, and isophthalic acid, was of the same order as obtained with unpromoted V_2O_5-kieselguhr catalyst.

Experiments conducted wth fused V_2O_5 catalyst showed that this catalyst gave appreciably higher conversion to aldehyde than the kieselguhr-supported unfused catalysts, reported above. The yields of other products were practically the same. At 550°, the fused V_2O_5-kieselguhr catalyst gave a conversion of 8.3% to tolualdehyde and 18.2% to maleic anhydride.

Mixed Xylenes.—The oxidation of mixed xylenes gave mainly aldehydes and maleic anhydride. About 18-20% of the xylenes passed were converted to maleic anhydride, whereas the total conversion to the water soluble acids was 22-25%.

(*b*) *Oxidation of Xylenes in the Fluidized Bed*

Bhattacharyya and Krishnamurthy[16] employed the fluidized bed of various catalysts for the same reaction and recorded some interesting results. Moreover, during the oxidation of the three xylenes, considerable amount of heat was liberated. Anticipating that these reactions, if carried out under practically isothermal conditions, might lead to improved yield and higher selectivity, they studied these reactions in fluidized bed with various vanadium oxide catalysts.

The vapour phase oxidation of *o*-xylene was studied in the fluidized bed with unfused and fused V_2O_5 catalysts, supported on various proportions of kieselguhr, and also with unfused promoted catalysts under a wide range of temperature, air/xylene ratio, space velocity,

volume of the catalyst, and concentration of CO_2 in the feed. The products obtained using fused catalysts were mainly phthalic anhydride, *o*-tolualdehyde, carbon dioxide, and traces of quinone whilst in the case of static bed, maleic anhydride was present instead of *o*-tolualdehyde. In the case of unfused catalyst in fluidized bed all the above products were found. Fused vanadium pentoxide afforded maximum yield of phthalic anhydride with high selectivity. Under the optimum condition (490°, air/xylene ratio=95.1; space velocity=10,030; volume of the catalyst=17.3 c.c.≈20g.) the conversion to phthalic anhydride was 67.8% and that to *o*-tolualdehyde was 3.56%, leading to a selectivity of 95%. One interesting feature with fused vanadium pentoxide catalyst in the oxidation of *o*-xylene under fluidized condition was that the yield of phthalic anhydride increased (with increase in concentration of xylene) when the air/xylene ratio was decreased from 2,230 to 102.5 and again fell down when the air/xylene ratio was further decreased to 53.9. Aldehyde yield fell down considerably when the air/xylene ratio was reduced. This effect was the reverse of that observed previously in the static bed.

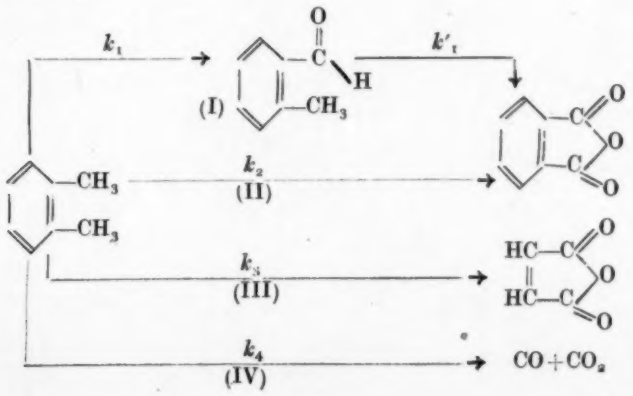
Similar studies were made with other catalysts and the result obtained thereby will be reported shortly.

In the case of oxidation of *p*-xylene, under the best condition and with fused V_2O_5 catalyst (465°, air/xylene ratio=365, space velocity=9,550), the conversions to various products are: terephthaladehydic acid=3.12%; terephthalaldehyde=19.32%; *p*-toluic acid=2.05%; *p*-tolualdehyde=19.91%; maleic anhydride=20.17%; quinone=5.18%. In the static bed terephthalic acid was present, whilst terephthalaldehyde and terephthalaldehydic acid were absent. Under optimum conditions (540°; air/xylene ratio=121.5; space velocity = 9,300), and using the same catalyst for influidized condition for oxidation of *m*-xylene, the following product distribution was obtained: Maleic anhydride=32.68%; *m*-tolualdehyde=10.82%; quinone=0.51%. In the static bed, in addition to the above products, isophthalic acid was present in traces.

The effects of space velocity, temperature, and air/xylene ratio on the oxidation of *o*-xylene, using fused V_2O_5 catalyst, both in the fixed and fluidized catalyst beds, are represented in Figures 2–4.

Very recently much attention has been focussed on the mechanism of this oxidation reaction and also on the role of the catalyst.

Simard *et al.*[17] have studied the kinetics of *o*-xylene oxidation at conversions below 25% over a SiC-supported V_2O_5 catalyst. They have suggested the following scheme of the reaction.



Reaction (I) was found to be first order with respect to *o*-xylene and *o*-tolualdehyde, whereas all other reactions were of zero order.

All the reactions showed a square root dependence on oxygen pressure. Hence it has been suggested that the uptake of oxygen is the rate controlling step.

Simard *et al.*[17] investigated the surface composition of vanadium pentoxide catalyst during the oxidation of *o*-xylene under normal operating conditions and concluded that the catalyst consisted of a mixture of V_2O_5, $V_2O_{4.34}$, V_2O_4 (and also V_2O_3 under certain conditions). Of these four different oxides, the first two were supposed to act as catalyst components.

Bhattacharyya and Gulati carried out the surface area measurement of various oxidation catalysts but did not find any correlation between the catalytic activity and the specific surface.

To ascertain the changes occurring in the catalyst during the reaction, the kinetics of oxygen adsorption was also studied over spent catalyst samples. A significant increase in the rate and amount of oxygen adsorption was observed in the case of spent catalysts. The results obtained by them have been discussed elaborately in a previous publication[2].

This kinetic study indicated that, during the oxidation reaction, the catalyst partly decomposed to a lower oxide; this was oxidised rapidly to the original oxide as soon as oxygen was introduced into the system at 520°. During the reaction, when air was present along with the *o*-xylene vapors, reoxidation of the catalyst occurred simultaneously with its reduction, setting up an equilibrium. Presumably, this equilibrium had almost been established when the *o*-xylene oxidation step was discontinued and the catalyst was flushed with nitrogen.

Even without passing the mixture of air and xylene, the fused vanadium pentoxide catalyst lost part of its chemically bound oxygen on being degassed at 520° and was reoxidised as soon as oxygen pressure in the system was increased. This indicated the mobility of oxygen in the vanadium pentoxide lattice at this temperature. In the presence of *o*-xylene, oxygen exchange between the gas phase and bulk phase was greatly facilitated because of the continuous reduction of the solid by the hydrocarbon.

Oxidation of Crotonaldehyde in the Fixed Bed

The catalytic oxidation of crotonaldehyde to maleic acid has not been investigated in any great detail. The only published work is that due to Faith and Schaible[18]. Using air/aldehyde ratio of about 300, the maximum conversion to maleic acid was reported as 42.2%, obtained with vanadium pentoxide deposited on aluminium granules. Much higher values for the conversion to maleic acid have been claimed in the patent literature. A systematic study of the vapour phase oxidation on crotonaldehyde to maleic acid in its manifold aspects was therefore undertaken by Bhattacharyya and his coworkers[19]. Only the salient features of their observations and the results of their recent investigations of fluidized bed synthesis have been discussed here.

Numerous catalysts consisting of the oxides of vanadium, molybdenum, tungsten, uranium and cobalt, supported on purified kieselguhr, were prepared by the familiar oxalic acid method, described in the discussion on the studies of oxidation of benzene. The vanadates of Ag, Sn, Bi, and Pb were obtained by the double decomposition between the soluble salts of the metals and alkali metavanadate. Each catalyst was subjected to a

mixture of crotonaldehyde and air/crotonaldehyde ratio=160 to 180, for at least 4 hours at 250-300° before its efficiency for the oxidation was studied.

Various V_2O_5-kieselguhr catalysts, promoted by UO_3, Co_2O_3, MoO_3, WO_3 and vanadates of Ag, Pb, Bi, and Sn, were tested for their catalytic activity.

The oxidation of crotonaldehyde to maleic acid could evidently be carried out fairly efficiently with a catalyst consisting of the oxides of vanadium and molybdenum, supported on purified Indian kieselguhr. (V_2O_5:MoO_3: Kg=38.9:686:100) or with a tin vanadate catalyst obtained by the double decomposition between aqueous solutions of stannous chloride and ammonium metavanadate.

At a space-velocity of about 12,000 l/hr./g., a process conversion of about 77% maleic acid was obtained with a catalyst consisting of the oxides of V and Mo supported on kieselguhr (Temp: 310° & air/aldehyde=150). Under similar conditions tin vanadate catalyst registered a process conversion of about 60% acid at the lower temperature of 230°.

From the studies of material balance it was concluded that besides the oxidation of crotonaldehyde to maleic acid and CO_2, crotonaldehyde was found to undergo decomposition and polymerisation losses appreciably.

The general behaviour of the catalysts with respect to various factors were found to be more or less similar in case of the oxidation of benzene and crotonaldehyde. It was surprising that the conversions to maleic acid obtained in the oxidation of crotonaldehyde were not as high as would be expected. This is particularly so in view of the fact that the molecule is expected to lend itself to oxidation with greater ease owing to the presence of easily oxidisable groups in it.

The effects of space velocity, temperature and air/aldehyde ratio on the conversion to and S.T.Y. of maleic acid using V_2O_5-MoO_3-kieselguhr, the best catalyst, are shown in Figs. 5-7.

Oxidation of Crotonaldehyde in Fluidized Catalyst Bed

Anticipating that the isothermal condition in a fluidized bed would lead to improved yield of maleic acid, Bhattacharyya and Kar[20] recently employed the fluidized catalyst bed for the oxidation of crotonaldehyde. They obtained very promising results and an extensive study in this line is still being pursued. Some of their encouraging observations are discussed below.

V_2O_5-MoO_3 (85:15), supported on pumice (28% total oxide), has been found to be the best catalyst for the reaction. Using this catalyst the conversions of crotonaldehyde to maleic acid at 325°, space velocity of 9022 c.c./hr./c.c. of catalyst and air/aldehyde ratios of 286, 444 and 700 were 66.87, 71.32, and 85.86% respectively. With further increase of air/aldehyde ratio, the actual conversion of crotonaldehyde to maleic acid increased, but space-time yield decreased. Carbon dioxide was the only byproduct of the reaction.

The conversions achieved by varying temperature, catalyst volume, air/aldehyde ratio, and space velocity, one at a time, are shown in Figs. 5-7.

Oxidation of Picoline to Nicotinic Acid in the Fluidized Bed

Catalytic oxidation of β-picoline to nicotinic acid, a valuable precursor of important medicines, either in the liquid phase or in vapour phase, has not been well studied and

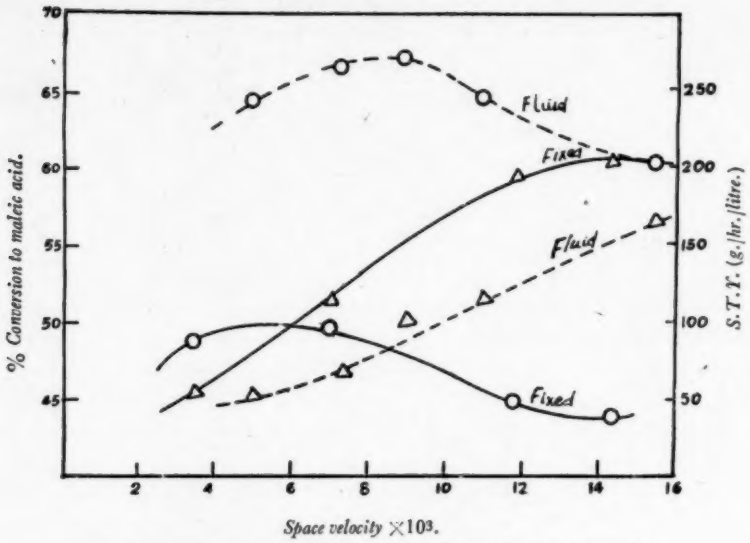


FIG. 5. Influence of space velocity on the conversion to maleic acid.
▲ : S.T.Y. O : % Conversion.

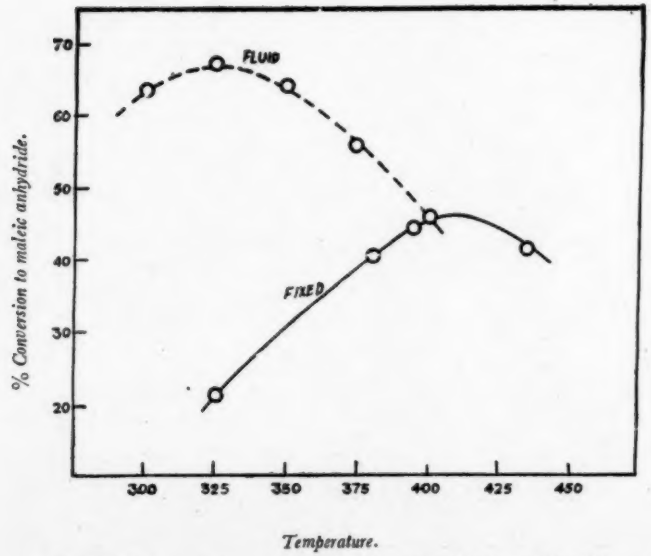


FIG. 6. Influence of temperature on the conversion to maleic acid.

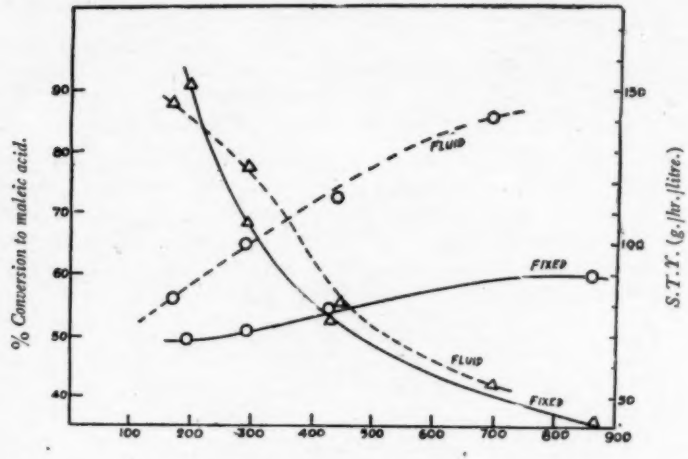


FIG. 7. Influence of air/aldehyde ratio on the conversion to maleic acid.

△ : S.T.Y. O : % Conversion.

most of the informations have been guarded in patent literature. Moreover, the production of nicotinic acid from β-picoline in the fluidized catalyst bed is exclusively unexplored. Its vapour phase oxidation to nicotinic acid was carried out by Bhattacharyya and Kar[20] in a fluidized catalyst bed of fused and unfused vanadium pentoxide. The influence of temperature, air/picoline ratio, and space velocity on the conversion of picoline to nicotinic acid was exhaustively studied. With the unfused V_2O_5: pumice (51.84: 100) catalyst the maximum yield of nicotinic acid was 16.65% (of theoretical) with 60 c.c. of catalyst under the optimum conditions of a temperature of 375°, air/picoline ratio of 225 and at a space velocity of 2395 c.c./hr./c.c. of catalyst. The percentage conversion of nicotinic acid on the basis of total picoline oxidised was 63.08%.

Using fused V_2O_5 on pumice (70:30) a maximum conversion of 24.37% (of theoretical) of β-picoline to nicotinic acid was achieved with 20 c.c. of catalyst at 490°, air/picoline ratio of 225, and at a space velocity of 5004 c.c./hr./c.c. of catalyst. The percentage conversion of nicotinic acid on the basis of total picoline oxidised was 51.42.

Further work in this line is in progress.

Conclusion

It has not been possible to discuss the oxidation of organic compounds in its full length within this short compass. The authors have concentrated mainly on the range of their work in this field. Besides the oxidation reactions reviewed here, oxidation of naphthalene, anthracene, acetylene, etc. has also drawn the interest of the scientists and technologists.

It has been quite clear that the application of fluidized catalyst technique, by facilitating uniform temperature distribution throughout the catalyst bed and by increasing the

available catalyst surface, has brought about considerable improvements in all the oxidation processes.

But it must be pointed out that this technique of fluidization favours only the reactions having high equilibrium constants; because otherwise, the equilibrium conversions are adversely affected due to the back-mixing of the products in the catalyst bed.

The studies on the physico-chemical properties of the important oxidation catalysts, by employing the techniques of X-ray diffraction, differential thermal analysis, semiconductivity measurements, adsorption measurements, etc. have recently evoked much scientific interest and have opened a new avenue for research. These investigations will surely evince the fundamental mechanism of contact catalysis as a whole, in all its intricacies and ramifications and thus will help the development of better catalysts.

Nomenclature

Space velocity (S.V.) *in c.c./hr./c.c* represents volume in c.c. of the inlet reaction mixture at N.T.P. flowing per hour per c.c. of the catalyst.

Contact time (*C.T.*) *in seconds*.—Volume of the catalyst in c.c./volume of the inlet gas mixture at the bed temperature and at the reaction pressure flowing per second.

Selectivity.—This is given by the relationship:

% Conversion of a reactant to the desired product $\times 100$/total conversion of the reactant.

Space-time yield (*S.T.Y.*) *in c.c./hr./c.c.*—Volume at N.T.P. of the product produced per hour per volume of the catalyst space.

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Initiators of Redox Polymerization

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The important observation was made in 1946 independently by Bacon[1], Evans and co-workers[2,18], Morgan[3], and others that an oxidation-reduction reaction can efficiently initiate polymerization. Such polymerization is called redox polymerization, the oxidant being often called the catalyst or initiator and the reductant, the activator. Some of the special features of redox polymerization are: (*i*) induction period is very short, (*ii*) a comparatively high molecular weight and high yield of polymers can be obtained in a very short time, (*iii*) activation energy is very small, (*iv*) the polymerization can be carried out at room temperature or below. An outcome of the redox-initiated polymerization is that it provides a direct experimental evidence of the existence of transient radical intermediates, generated in redox reactions, and identification of these radical end-groups in the resulting polymer throws new light on the reaction mechanism of redox reactions. It is the purpose of the present article to review the various redox systems, which have been used in such polymerization, with special reference to the initiating radical, and identification thereof by methods recently developed in this laboratory[7,9,4].

General Reaction Mechanism of Free Radical Initiated Polymerization

As the name suggests, the initiating species of the type of vinyl polymerization is essentially a free radical, generated in the redox reaction, and the reaction mechanism is governed by the laws of free radical reactions (*i.e.* chain reaction). Three steps are involved, e.g., initiation, propagation, and termination. But the fundamental difference between the chain reactions involved in vinyl polymerization and in classical hydrogen-chlorine combination lies in the fact that in the latter case chain carriers have the same size, but in the former case, chain carriers have different sizes, although it is assumed that radical reactivity is independent of chain length in polymerization processes.

If R· be a free radical, and M be a monomeric entity, the steps of the chain reaction are:

Initiation: $M + R\cdot \longrightarrow R-M\cdot$

Propagation: $R-M\cdot + M \longrightarrow R-M-M\cdot$

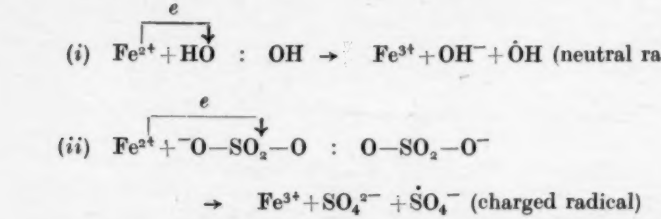
$R-M\cdot_n + M \longrightarrow R-M\cdot_{n+1}$

Termination: $R-M\cdot_n + \cdot M_m-R \longrightarrow R-M_{m+n}-R$ (by combination)

$R-M\cdot_m + \cdot M_n-R \longrightarrow R-M_m + M_n-R$ (by disproportionation)

Besides, termination may also take place by chain transfer to monomer, to solvent, or to any reactive species like catalyst, activator, inhibitor, or retarder molecules and even by collision between a chain radical and a primary radical, generated from redox reactions.

The free radicals may be neutral or charged. For example,



(*i*) $Fe^{2+} + HO : OH \rightarrow Fe^{3+} + OH^- + \dot{O}H$ (neutral radical)

(*ii*) $Fe^{2+} + {}^-O{-}SO_2{-}O : O{-}SO_2{-}O^-$

$\rightarrow Fe^{3+} + SO_4^{2-} + \dot{S}O_4^-$ (charged radical)

In both cases, Fe^{2+} ion donates one electron to a molecule of the oxidant, as a result of which the latter becomes thermodynamically unstable and breaks up with the production of a radical.

These radicals open the double bond of the molecules of vinyl monomer (CH_2=CHX or CH_2=CXY) and thereby attach themselves to the end of the polymer chains as end groups. The presence of these end groups or initiator fragments in polymer chains has been proved by tracer technique[5,3,9,8,1], chemical analysis[6], and recently by 'dye[6] partition test'[7,9,0].

Some Aspects of Aqueous Polymerization

Redox-initiated vinyl polymerization in aqueous medium may be of two types, e.g., polymerization of (*i*) water-soluble monomers within their solubility range and (*ii*) both water-soluble and water-insoluble monomers in presence of detergents.

The nature of the polymerization reactions depends on the structure of the monomer, the affinity of the monomer to its polymer, degree of swelling of the polymer with its monomer, etc. It has been noted that monomers like vinyl acetate, methyl methacrylate, methyl acrylate, etc. can be polymerised up to 90 to 92% conversion, but acrylonitrile cannot be polymerised beyond 40 to 45% conversion whatever may be the nature of the redox species. This low conversion is possibly due to the fact that the monomer concentration at the reaction site is low, as the polyacrylonitrile particles are not at all swollen by acrylonitrile monomer, only a very small fraction of it gets adsorbed on them[8,80]. Again, vinyl acetate polymerises at a faster rate than any other water-soluble monomer, even faster than methyl acrylate, which is possibly due to both polar and steric factors and to the differences in resonance stabilization of the monomer and the radical. The rate of styrene polymerization is comparatively slow, possibly due to the resonance stability of the propagating styryl radical, and lastly ethylene polymerization is a very difficult job. Thus the structure of the monomer plays an important role in polymerization.

Apart from the monomeric entity, other rate-controlling factors are: (1) redox pair, (2) *p*H of the medium[1], (3) temperature, (4) agitation after initiation, (5) oxygen content of the medium, etc. The separating phase after initiation also plays a very important role in heterogeneous polymerization. If the separating phase is a fine sol, the rate will be higher than that of the case when the separating phase is a coarse coagulum[9]. Polymerization rate generally increases with the rise of temperature as is expected from the Arrhenius theory, but many conflicting reports are available in the literature. For example, Bacon[1] and Whitby *et al.*[10] reported that the rate of polymerization would rise with temperature, whereas work in our laboratory[11] shows that the rate of polymerization attains a maximum value at 45° and then falls with further rise in temperature. This discrepancy is pos-

sibly due to the nature of the initiator used and degree of stability of the separating phase. Agitation after initiation depresses the rate, as has been reported by many workers[12], which is probably due to aggregation of the particles carrying the reaction loci.

Detergents function in two ways, viz., (1) they increase the solubility of the monomer by emulsifying it[13] and (2) they protect the polymer particles from coalescence by acting as peptisers[2,14]. Thus detergent action is purely physical and the kinetics of methyl methacrylate polymerization remains the same in presence and absence of cetavlon[14], provided that the monomer concentration exceeds its solubility in the aqueous phase. But Kolthoff and Miller[15] showed that fatty acid soaps, when used as emulsifier in emulsion polymerizations using $K_2S_2O_8$ as initiator, underwent chemical change such as decarboxylation.

Initiation by Redox-reaction Involving One-electron Change

To this class belong both organic and inorganic peroxide systems, hydroperoxide systems, and systems containing non-peroxidic substances as redox components.

Hydrogen Peroxide Systems.—Evans and his school[2] studied Fenton's reagent ($FeSO_4$–H_2O_2) as a redox initiator where OH· radicals are known to be the chain-initiating species. The mechanism of this redox reaction is primarily due to Haber and Weiss[16]. In presence of monomer, there is a competition between the monomer and the unchanged ferrous ions for consuming the hydroxyl radicals. In presence of a sufficient amount of monomer, no evolution of oxygen occurs and ferrous ions react according to equation (*i*). In the absence of monomer, the reaction takes place as follows, where (*i*) is the initiation reaction, (*ii*) and (*iii*) or (*ii*), (*iv*) and (*v*) are the chain decomposition of H_2O_2, (*vi*) is chain termination, and (*vii*) is the initiation of polymerizantion.

$$Fe^{2+} + HO\text{–}OH \longrightarrow Fe^{+3} + OH^- + \cdot OH \qquad (i)$$

$$\cdot OH + H_2O_2 \longrightarrow H_2O + HO\cdot_2 \qquad (ii)$$

$$HO\cdot_2 + H_2O_2 \longrightarrow \cdot OH + O_2 + H_2O \qquad (iii)$$

$$HO\cdot_2 \rightleftharpoons O_2^- + H^+ \qquad (iv)$$

$$O_2^- + H_2O_2 \longrightarrow O_2 + OH^- + \cdot OH \qquad (v)$$

$$Fe^{2+} + \cdot OH \longrightarrow Fe^{3+} + OH^- \qquad (vi)$$

$$\cdot OH + \begin{array}{|c|c|}\hline | & | \\ \hline | & | \\ \hline \end{array}\!\!C{=}C\!\!\begin{array}{|c|c|}\hline | & | \\ \hline | & | \\ \hline \end{array} \longrightarrow HO\text{–}\begin{array}{|c|c|}\hline | & | \\ \hline | & | \\ \hline \end{array}\!\!C\text{–}C\!\!\begin{array}{|c|c|}\hline | & | \\ \hline | & | \\ \hline \end{array}\cdot \qquad (vii)$$

Evans and coworkers[17] showed that oxidation of glycolic acid by $FeSO_4$–H_2O_2 was greatly reduced in presence of acrylonitrile. This indicates that ·OH radicals are responsible for both polymerization and oxidation.

Again, if ·OH radicals be the chain-initiating species, OH groups must be present in the polymer as end groups. This has been proved by Evans[18] by infrared absorption spectra[19] and recently in our laboratory by the 'dye partition test'[20].

Barb *et al.*[95] modified the Haber-Weiss mechanism and showed that oxygen evolved according to the following reaction, and not due to reaction (*iii*).

$$Fe^{3+} + HO\cdot_2 \longrightarrow Fe^{2+} + O_2 + H^+$$

$Fe^{2+}-H_2O_2$ system, however, does not always initiate polymerization. For example, Barb *et al*[95] failed to initiate acrylonitrile polymerization under the following conditions: (*i*) Fe^{2+} concentration $=10^{-4}$, H_2O_2 conc.$=1.0$ *M*, *p*H$=1$, and *N*/5 acrylonitrile at 25°. The excess hydrogen peroxide removes the hydroxyl radicals from the medium according to reaction (*ii*), and HO_2· radicals, thus formed, do not initiate vinyl polymerization. In other words, at a fixed concentration of the activator, there is a fixed concentration of catalyst for polymerization to occur. Marvel *et al.*[21] studied copolymerization of butadiene and styrene, whereas Kern[12] reported the same copolymerization using H_2O_2—Fe^{2+} ions—sorbose as initiator. Like Fe (II) salts, Fe (III) salts are also effective in activating hydrogen peroxide; both the salts are equivalent in their activating effect[21].

According to Marvel *et al.*[21] the reaction between ferric ions and hydrogen peroxide is believed to be as follows:

$$Fe^{2+} + HOOH \rightarrow Fe^{3+} + OH^- + \cdot OH$$
$$Fe^{3+} + HOOH \rightarrow Fe^{2+} + \cdot OOH + H^+$$
$$\cdot OH + HOOH \rightarrow H_2O + \cdot OOH$$
$$\cdot OOH + H_2O_2 \rightarrow O_2 + H_2O + \cdot OH$$

Dainton *et al.*[8,12a] studied acrylonitrile polymerization initiated by Fenton's reagent. They noted that whenever ferric salts were either present initially or generated *in situ*, some polyacrylonitrile radicals were always destroyed by Fe^{3+} ions. The rate of polymerization is proportional to the square of the monomer concentration at low monomer concentrations and linearly dependent on monomer concentration at high monomer concentrations.

Hydrogen peroxide has also been activated by various reducing agents. It appears that the mechanism is essentially the same, involving ·OH radicals. Some such typical activating agents are ammonia or aliphatic amines[23], sodium nitrite[24], formic acid and ferrous ammonium sulphate[23], acetic acid and ferrous sulphate[4,5], Rongalite[27], ferric nitrate[27a], ferrous ammonium sulphate in presence of potassium palmitate, E.D.T.A. and other complexing agents[27b], and peroxidase[27c]. Bacon[1] reported activation of H_2O_2 by $NaHSO_3$ in the polymerization of acrylonitrile in aqueous solution. Kern *et al.*[85] reported acrolein polymerization using (*i*) hydrogen peroxide-ferrous ammonium sulphate, (*ii*) H_2O_2–$AgNO_3$, and (*iii*) H_2O_2–$NaNO_2$, as redox initiators.

In the system H_2O_2—CH_3COOH—$FeSO_4$, the radicals are both ·OH and $\cdot CH_2COOH$, the presence of the latter having been proved in our laboratory by the dye-test[84]. This accounts for the observed retarding action of acetic acid on the Fe^{2+}–H_2O_2 reaction[26].

$$Fe^{2+} + HOOH \rightarrow Fe^{3+} + OH^- + \cdot OH$$
$$CH_3COOH + \cdot OH \rightarrow \cdot CH_2COOH + HOH$$

Persulphates.—Persulphates, either alone or with activators, have been extensively used as initiators of redox polymerization. Bacon[1] activated persulphate using various reducing agents, viz., metals, oxidisable metal salts, hydrazine, hydroxylamine, hydrogen sulphide, thiols, salts of various oxyacids of sulphur (sulphite, dithionite and thiosulphate), and polyhydric phenols. Kern[4] also reported similar observations. Kolthoff *et al.*[28] and Williams *et al.*[29] studied the kinetics of polymerization initiated by $S_2O_8^{2-}$—Fe^{2+} ions. Activation of persulphates has also been done by ferricyanide[30] and various cobalt complexes[31]. The details of the reactions are not available; the system is also very complex as these multivalent metal ions can initiate polymerization without the aid of peroxidic substances[32,32a]. Tervalent silver, when added in the form of biguanide complex[96], can initiate polymerization of acrylonitrile and methyl methacrylate[84]. Silver ion—persulphate (Ag^+-$S_2O_8^{2-}$) is also a very useful redox initiator and has been used by many workers [1,3,16,33].

In copolymerization of styrene and butadiene, the initiators that have been used extensively are thiol-persulphate[34] and bisulphite-persulphate[35]. Some metal ions and also anions act as promoters in the two-component 'reduction-activation' of persulphates, e.g., Fe^{2+}, Cu^{2+}, I^- ions in $S_2O_8^{2-}$—$S_2O_3^{2-}$ system[3], Fe^{2+} in $S_2O_8^{2-}$—HSO_3^- (used for tetrafluoroethylene[39] polymerization) and silver (used for chlorotrifluoroethylene[40] polymerization). Roskin[41] used the $S_2O_8^{2-}$—$S_2O_4^{2-}$ redox pair; Palit and Guha[43] and Palit and Biswas[44] used the same for aqueous redox polymerization. Acrolein has been polymerised by the initiator $S_2O_8^{2-}$—SO_3^{2-}, $S_2O_8^{2-}$—NO_2^-, $S_2O_8^{2-}$—Ag^+, $S_2O_8^{2-}$—Ti^{3+} by Kern *et al*[42].

As to the mechanism of initiation, the general trend is to assume an electron transfer as in Fenton's reaction, giving rise to an $\cdot SO_4^-$ ion radical, e.g.,

$$Fe^{2+} + S_2O_8^{2-} \longrightarrow Fe^{3+} + SO_4^{2-} + \cdot SO_4^-$$

The initiation by ·OH radicals has also been suggested by Morgan[3] and Whitby *et al.*[10] in the Ag^+—$S_2O_8^{2-}$ system, but others consider $\cdot SO_4^-$ to be the initiating radical[1]. Roskin[41] also propounds the ·OH radical in the $S_2O_8^{2-}$—$S_2O_4^{2-}$ system.

$$S_2O_8^{2-} + S_2O_4^{2-} + 2H_2O \longrightarrow 3SO_4^{2-} + S + 2H^+ + 2\dot{O}H$$

Eager and Winkler[36] studied the kinetics of the thiol-persulphate reaction in homogeneous aqueous solution and formulated it as:

$$S_2O_8^{2-} \overset{\text{slow}}{\rightleftharpoons} 2\,\dot{S}O_4^-$$

$$RSH + \dot{S}O_4^- \underset{\text{fast}}{\longrightarrow} HSO_4^- + R\dot{S}$$

Levitt[36] believed that sulphur tetroxide was an intermediate product in this reaction. Like thiols, thiol-esters[37] and diaroyl disulphides[37] may be used in the activation of persulphate in the copolymerization of butadiene and styrene. Kolthoff *et al.*[38] also used persulphate-thiol redox in the emulsion polymerization of vinyl monomer. Campbell[86] studied polymerization of acrylonitrile, initiated by $K_2S_2O_8$—$NaHSO_3$, in presence of various complexing agents for iron, which is always present as trace impurities in the catalyst, and the activator. He demonstrated that $S_2O_8^{2-}$—HSO_3^- reaction would always require a trace of iron as catalyst. $K_2S_2O_8$—ferrous ammonium sulphate has been used in the polymerization of methylvinyl ketone[10].

In may be pointed out that the evidence for the varied types of suggested initiating radical had so far been highly conjectural, resting on kinetic evidence based on none-too-reproducible data. Direct evidence has been lacking except in a few cases where the existence of sulphur in the polymer has been demonstrated and even measured, using tracer techniques[5]. The position has lately become, however, more definite by the development in our laboratory of two simple methods[7,94] of detection of end groups by interaction with dyes. The results of end-group detection show that SO_4^- radicals are not necessarily the initiator in many redox systems containing $S_2O_8^{2-}$. For example, we have found that polymers, obtained by initiation with $S_2O_8^{2-}$ alone and $HCOO^-$—$S_2O_8^{2-}$ system, contain no strong acid end group, but $S_2O_8^{2-}$——Ag^+,-$S_2O_8^{2-}$—$S_2O_3^{2-}$ and $S_2O_8^{2-}$—$S_2O_4^{2-}$ initiated polymers give positive test for strong acid end group. The question seems to be an intriguing one and the matter is being closely investigated in our laboratory.

Organic Peroxide and Hydroperoxide Systems.—The initiation of vinyl polymerization by organic peroxide systems is primarily due to the German workers and later on by the American workers for industrial processes. Kern[4,41] has reported a large number of redox systems containing benzoyl peroxide. The general reaction mechanism in the three-

component systems (organic peroxide—Fe^{2+} ions—a reducing agent YH_2) is believed to be as follows:

$$Fe^{2+}(R.COO)_2 \longrightarrow Fe^{3+} + RCOO^- + RCOO\cdot$$
$$Fe^{3+} + YH_2 \longrightarrow Fe^{2+} + YH\cdot + H^+$$
$$Fe^{3+} + YH\cdot \longrightarrow Fe^{2+} + Y + H^+$$
$$RCOO\cdot + YH_2 \longrightarrow RCOOH + YH\cdot \text{ etc.}$$

When the reducing agent does not react with Fe^{3+} ions, the metal ions function by complex formation with the reducing agent (e.g., benzoyl peroxide—Fe^{3+} ions—tertiary amine[45]):

$$Fe^{2+} + XH \longrightarrow Fe^{2+}\ (XH)$$
$$Fe^{2+}(XH) + (R.COO)_2 \longrightarrow Fe^{2+}\ (X) + RCOO\cdot + R\ COOH$$
$$Fe^{2+}\ (X) \longrightarrow Fe^{2+} + X$$

The chain initiating species are RCOO· radicals[46]. Marvel *et al.*[47] and Johnson and Bebb[48] studied copolymerization of butadiene and styrene using benzoyl peroxide and acetyl peroxide systems. The reducing agents of the three-component peroxide systems are α-ketols, benzoin, dihydroxyacetone, or preferably ketoses (sorbose and fructose). Wall and Swoboda[49] have used benzoyl peroxide—iron pyrophosphate—sorbose as redox initiator. This system has also been studied by Kolthoff *et al* [50].

The bulk polymerization of vinyl monomers by redox pairs like benzoyl peroxide and a reducing agent like sulphinic acids, α-ketols, formic acid, thiols, hydrazines, and tertiary amine had been studied[45]. The activity of such systems is greatly enhanced by the introduction of a soluble metal salt (salts of Pb, Fe, Co, Ni, Mn, Cu, Zn, Ce).

Hasegawa *et al.*[51] studied vinyl acetate polymerization using benzoyl peroxide—Fe^{2+} ions—benzoin system. Kern[52] studied styrene polymerization using the same system. Tobolsky *et al.*[53] and O'Driscoll *et al.*[54] studied 'Dead end polymerization' of vinyl monomers using benzoyl peroxide—dimethylaniline as redox pair. This redox pair has also been used by many other workers[91,92,93] for studying the polymerization of styrene and methyl methacrylate.

Hydroperoxide Systems.—Like organic peroxides, hydroperoxides (e.g. cumene hydroperoxide) have been used extensively in vinyl polymerization in presence of a suitable reducing agent. In presence of metal ions as reducing agent, the hydroperoxide is decomposed as a free radical[55-56].

$$Fe^{2+} + Ph.CMe_2OOH \longrightarrow Fe^{3+} + Ph.CMe_2O\cdot + OH^-$$
$$Co^{2+} + Ph.CMe_2OOH \longrightarrow Co^{3+} + Ph.CMe_2O\cdot + OH^-$$
$$Co^{3+} + Ph.CMe_2OOH \longrightarrow Co^{2+} + Ph.CMe_2OO\cdot + H^+$$

But in alkaline medium, decomposition of cumene hydroperoxide by Fe^{2+} ions has been reported to be ionic in character[57].

A large number of reducing agents have been used in conjunction with cumene hydroperoxide and iron salts, e.g., dihydroxyacetone, sodium sulphide, hydrazine, sodium formaldehyde sulphoxylate[58]. Cumene hydroperoxide—Fe^{2+} salts—sugar also has been used in styrene—butadiene copolymerization[59]. Fe-salts have been used in the form of pyrophosphate[59] or E.D.T.A. complex[60].

Kolthoff *et al.*[61] studied a complicated reaction involving isopropyl-$\alpha\alpha$-dimethylbenzyl hydroperoxide—nitroprusside—hydroxylamine—thiol as initiator of polymerization. Orr and Williams[62] studied the reaction kinetics of cumene hydroperoxide—Fe^{2+} salts—amine (e.g. diethylenediamine, triethylenetetramine, or tetraethylenepentamine) in presence and absence of methyl methacrylate and found that Fe^{2+} ions formed complexes with the amine; this complex subsequently reacted with the hydroperoxide.

$$ROOH + R'NH_2A \longrightarrow RO\cdot + R'NH + H_2O + A$$
$$[A = Fe^{2+},\ Fe(OH)^{+},\ \text{or}\ Fe(OH)_2]$$

Isopropylbenzene hydroperoxide—SO_2 redox system has been used in emulsion polymerization[63]. Polyamines [NH_2—(CH_2·CH_2NH)$_n$–H],—cumene hydroperoxide—Fe^{2+} salts have also been used as initiator of polymerization[70].

System Containing Air or Oxygen.—The role of oxygen in aqueous and emulsion polymerization of vinyl monomers has been discussed by Kern[4] and by Bovey and Kolthoff[64], and recently by Dainton[8]. It has been established that induction period in polymerization is primarily due to oxygen, which thus acts as an inhibitor. But if the reducing agent of the redox system is reactive towards oxygen, the induction period will be shortened and the oxygen will behave as a co-catalyst. Sully[65] reported that the emulsion polymerization of styrene was promoted by sulphite in presence of traces of air and copper salt

$$Cu^{2+} + SO_3^{2-} \longrightarrow Cu^{+} + \cdot SO_3^{-}$$

The Cu^{+} ions are again reoxidised by air. We have also noted that potassium bisulphite in presence of traces of air can initiate polymerization of methyl methacrylate, strong acid end groups having been detected in the polymer[84]. The probable reaction is

$$4HSO_3^{-} + O_2 \longrightarrow 4\cdot SO_3^{-} + 2\ H_2O.$$

German workers[66] have studied copolymerization of butadiene—styrene, using oxygen as sole oxidant in different redox systems. The reducing agents were dithionite, sulphinic acids, thiols and α-ketols, promoted by iron pyrophosphate. Marvel[67] extended the same work, using cobalt salt as additional catalyst and long chain alkane-1-sulphinic acid as a reducing agent.

Hydrazine—Cu^{+} ions—oxygen has been used as a three-component redox initiator by Menon and Kapur[68]. The reactive species are believed to be hydrazyl radicals.

Oxygen also acts as a chain-terminating agent by forming peroxides[2,4,69].

Non-peroxidic Systems.—Fe^{3+}—HSO_3^{-} and Fe^{3+} —$S_2O_3^{2-}$ systems have also been used as redox initiators[72]. The probable reactions are:

$$Fe^{3+} + HSO_3^{-} \longrightarrow Fe^{2+} + \dot{H}SO_3$$
$$Fe^{3+} + S_2O_3^{2-} \longrightarrow Fe^{2+} + \cdot S_2O_3^{-}$$

We have also used Fe^{3+}—$S_2O_3^{2-}$ system for initiation of methyl methacrylate polymerization in aqueous solution, strong acid end groups having been detected in polymers[84].

Davies *et al.*[73] reported that hydroxylamine—titanous/chromous salt in acid solution could initiate polymerization and they proved that initiation was due to $\cdot NH_2$ radicals.

$$Ti^{3+} + \dot{N}H_3OH \longrightarrow Ti^{4+} + \dot{N}H_2 + (OH^{-}—H^{+})$$

Evans and co-workers[74] showed that Fe^{3+} salts—hypobromous acid could initiate polymerization and that bromine atoms initiated the chain reaction.

$$Fe^{2+} + HOBr \longrightarrow Fe^{3+} + OH^- + Br.$$

Acrylonitrile[75,1] was polymerized by the redox pair, trimethylamine and chlorine.

$$ClNMe_3^+ + Cl^- \rightleftharpoons NMe_3 + Cl{:}Cl$$
$$NMe_3 + Cl{:}Cl \longrightarrow NMe_3^+ + Cl^- + Cl$$

Ceric nitrate—3-chloro-1-propanol has been used in the initiation of acrylamide[76]. Ceric salts and organic reducing agents, e.g., alcohols, thiols, glycols, aldehydes, and amines, have been used in the preparation of graft copolymer[87]. Ceric ion proceeds *via* a single-electron transfer with the formation of free radicals on the reducing agent[87].

$$Ce^{4+} + RCH_2OH \rightleftharpoons [\text{activated complex}]$$
$$\downarrow$$
$$Ce^{3+} + H^+ + \dot{R}CHOH$$

Ceric ion—alcohol (e.g. ethyl, amyl, etc.) has been used for the initiation of vinyl monomers by Santhapa *et al*[77].

Methyl methacrylate has been polymerized by xanthine oxidase (OX) and formaldehyde[78].

$$OX + CH_2(OH)_2 \rightleftharpoons XOH + CH_2(OH)-O\cdot$$
$$XOH + M \text{ (monomer)} \longrightarrow H\text{-}M\cdot + OX^-$$
$$CH_2(OH)-O\cdot + M \longrightarrow H-M\cdot + HCOOH.$$

Peroxidase—H_2O_2 has also been used as polymerization initiator[79]. *N*-Nitrosoacetanilide and ferrous versenate or citrate[88] have been used in the emulsion polymerization of styrene and in the styrene—butadiene emulsion copolymerization. Diazonium compounds and metal ions[89] can also initiate vinyl polymerization.

Reactions Involving Multi-electron Change

In this system the oxidant must contain an atom existing in a higher state of oxidation, e.g., Mn in permanganate and MnO_2, Cl in chlorate and chlorite, Br in bromate, etc. Kern[4] reported that German workers used chlorate, hypochlorite, permanganate, or manganese dioxide as the oxidising agent of redox initiators, but details are not available.

Kolthoff and Meehan[71] reported that initiation of butadiene-styrene copolymerization could be done by unstable ionic species. They used chromate-arsenite system for initiation and proposed the following redox reaction:

$$Cr^{6+} + As^{3+} \longrightarrow Cr^{4+} + As^{5+}$$
$$Cr^{4+} + M \text{ (monomer)} \longrightarrow Cr^{3+} + M\cdot$$
$$Cr^{6+} + Cr^{4+} \longrightarrow 2Cr^{5+}$$
$$Cr^{3+} + M \longrightarrow (Cr^{5+}M)$$

Possibly both Cr^{4+} and Cr^{5+} ions are the initiating species.

Thomas *et al.*[80] studied acrylonitrile polymerization kinetically, using ClO_3^-—SO_3^{2-} system in acid solution. Firsching and Rosen[81] used ClO_3^-—HSO_3^- redox, and they, by using tracer techniques, showed that the initiating species were $\cdot SO_3^-$ and $Cl\cdot$ radicals.

We have used a large number of redox initiators containing permanganate as the oxidising agent. The reducing agents are oxalic acid [82,90] citric acid, tartaric acid, isobutyric acid, glycerol[90], bisulphite[84] (in presence of dilute H_2SO_4), hydrosulphite[84] (in presence dilute H_2SO_4), etc. In case of organic acids, carboxyl end groups[7] have been identified in polymers, OH end groups[7] in case of glycerol as reduction activator, and strong acid end groups[84] in case of bisulphite, sulphite and hydrosulphite. The peculiarity of the permanganate system is that there are two consecutive redox systems in presence of monomer[84], viz., (1) permanganate (oxidant) and monomer (reductant); and (2) separated manganese dioxide (oxidant) and added reducing agent (reductant).

In case of permanganate—oxalic acid, the reactive species may be any one of the following: carboxyl ion radical, oxalate ion radical, (HCO_2, HC_2O_4) and possibly the radical containing manganese, as postulated by Duke[83a]. This is consistent with the fact that the reaction solution absorbs oxygen[83].

We also noted that freshly prepared MnO_2—H_2SO_4 is a very good redox initiator, sulphate end groups having been detected in the polymers[84],

$$MnO_2 + 2\,SO_4^{2-} + 4\,H^+ \longrightarrow Mn^{2+} + 2\,\dot{S}O_4^- + 2\,H_2O$$

This $\dot{S}O_4^-$ radical possibly initiates the polymer chain. $KBrO_3$—$KHSO_3$, and $KBrO_3$—Na_2SO_3—H_2SO_4 redox systems[84] can also initiate polymerization, giving rise to strong acid end groups in the polymer.

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Studies on Ascorbigen

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It was observed quite a long time back that certain vegetable materials gave a higher value for ascorbic acid, as estimated by titration with 2,6-dichlorophenol indophenol, when they were heated for a short period with water[1]. These increased values were observed particularly in the cases of turnips, carrots, beets, potatoes, cauliflower and cabbage. The explanation offered was that some ascorbic acid was present in these foodstuffs in a bound form, from which it was released by hydrolysis.

Guha and Pal[2] confirmed these results in regard to cabbage and a few other plant materials and termed the bound ascorbic acid as "ascorbigen" for brevity. Some workers[3-5] were of the opinion, however, that the observed increase in ascorbic acid value on heating with water was due to the thermal destruction of ascorbic acid oxidase present in these plant materials, which normally oxidises ascorbic acid when the material is crushed, thus giving low values of ascorbic acid. Pal and Guha[6], however, provided considerable evidence to indicate the existence of ascorbigen. They prepared absolute alcohol extracts of cabbage after macerating it with anhydrous sodium sulphate and found that on heating the extracts on a boiling water bath the indophenol-reducing value was considerably increased. They found that ascorbigen was quite labile and would release ascorbic acid at the *p*H of gastric juice. They, however, found that all vegetables and fruits did not contain ascorbigen but the *Brassica* group of vegetables contained considerable quantities of this substance. This work was further extended by Sen Gupta and Guha[7] and it was observed that among the different solvents used for extracting ascorbigen from dried cabbage, chloroform was the most efficient. The extracts were found free from ascorbic acid and dehydro-ascorbic acid. The aqueous solutions of the dried chloroform extracts, when heated on a water-bath for 10 minutes in an atmosphere of nitrogen, produced a considerable quantity of indophenol-reducing substance or substances. Chloroform would not extract ascorbic acid oxidase and the extract also did not show its presence on treatment with ascorbic acid. The value of the reducing substances obtained on heating the chloroform extract could not therefore be in anyway connected with the thermal inactivation of ascorbic acid oxidase. It was further observed that 60-70% of the reducing substances, produced by heating the aqueous solutions of the dried chloroform extract, disappeared when these were treated with an ascorbic acid oxidase preparation from cucumber. This would indicate that 60-70% of the reducing substances represent ascorbic acid; the rest apparently represents some non-specific reducing substances. Biological experiments with scorbutic guinea pigs showed that the chloroform extracts, which were free from ascorbic acid, were active and their activities were roughly comparable with equivalent amounts of pure ascorbic acid. Exact correspondence could not be expected as about 30% of the reducing substances produced from chloroform extracts by heat appeared to be non-specific. Sen

Gupta, Sarkar and Guha[8] confirmed these results by carrying out biological experiments by using the histological tooth method in which the degree of protection to predentine given by ascorbic acid was measured.

Ghosh and Guha[9] carried out a series of experiments for concentrating ascorbigen from cabbage juice. Protein precipitating reagents did not precipitate ascorbigen. It was observed, however, that norite 'charcoal' and active 'charcoal' would adsorb 60% of the ascorbigen from fresh cabbage juice. It was possible to elute the larger fraction of ascorbigen from this adsorbate by gently heating it with 70:30 chloroform-alcohol mixture. The extract was evaporated in a vacuum desiccator and it was taken up with the minimum quantity of water and centrifuged. The centrifugate was evaporated to dryness in vacuum and on heating its aqueous solution it was found to release indophenol-reducing substances, 60% of which was oxidised by ascorbic acid oxidase. The rest apparently represented non-specific reducing substances. The ascorbigen preparation could be further concentrated by means of sodium tungstate. The active preparations gave positive tests for carbohydrates and negative tests for proteins. The materials, however, were obviously still impure.

McHenry and Reedman[10] carried out chemical, spectrophotographic, and biological experiments with potato. They obtained similar evidence for the presence of the bound form of ascorbic acid in potato.

This problem was not much pursued, however, during the war years, but interest in the subject revived after the war, particularly in the Soviet Union and Czechoslovakia. Sumstov[11] and Terent'eva[12] substantially confirmed the results obtained by Guha and co-workers. They also obtained active extracts from cabbage juice by the charcoal absorption method and they also demonstrated the biological activity of their ascorbigen preparation by experiments with guinea pigs.

Striking advances in the subject were made in post-war years by Prochazka and his co-workers[13]. They identified the presence of ascorbic acid in the hydrolysate of a preparation of ascorbigen by paper chromatography. On paper chromatogram the ascorbic acid released from ascorbigen showed the same R_f value as that of pure ascorbic acid. Prochazka *et al.*[14] have reported the isolation of pure ascorbigen from cabbage (yield about 5 mg. per kg. of cabbage) and they have given it the empirical formula $C_{17}H_{17}O_7N$. Its melting point was reported to be 86-89°. Although it was amorphous, it was said to give crystalline derivatives with picric acid and diazomethane. They considered that the ascorbigen molecule consisted of ascorbic acid and an indole moiety, as hydrolysis of the substance yielded ascorbic acid and another component giving the Ehrlich test for indoles. Since then Prochazka and Severa[15] have described an improved process for the isolation of ascorbigen.

This investigation was resumed in recent years in this laboratory. Malakar and Guha[16] have isolated a material from cabbage juice whose empirical formula agrees with that for ascorbigen given by Prochazka *et al.*[14,15] and its melting point is 84°. It also splits into ascorbic acid and an indole moiety giving the Ehrlich reaction. Its absorption spectra also agree with those given by Prochazka *et al*[15].

The method consists of adsorbing ascorbigen of cabbage juice with active carbon, eluting it with a mixture of chloroform and rectified spirit (7:3), concentrating the extract *in vacuo* and subjecting it to chromatography in a silica gel column, and fractionating the

active material by gradient elution with ethyl acetate and chloroform. The richest fraction yielded a white amorphous substance which gave on hydrolysis 50% of its weight as ascorbic acid.

The ascorbigen so isolated has been investigated chromatographically both before and after hydrolysis by Bose and Guha[17] and ascorbic acid and an indole compound as moieties of the ascorbigen molecule have been confirmed. Bose and Guha[17] have also shown the presence of ascorbigen by the chromatographic procedure not only in *Cruciferae*, of which the *Brassica* group contains a considerable quantity of it, but also in certain non-cruciferous plants, particularly chillies and bitter gourd.

The biological role of ascorbigen in plants is under investigation both in Prague[18] (Kutacek *et al.*) and in this laboratory. Preliminary experiments indicate its rise and fall at different stages of growth and flowering, which might be related to its requirement or otherwise at different stages of metabolism.

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Life-times of Excited States of Molecules and their Determination

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When a radiation of proper frequency falls on a system of oscillators, it is absorbed by them and the latter are transferred to higher energy levels according to certain rules. The oscillators cannot stay, however at this excited energy level for an indefinite length of time and must return to the ground state. The time spent by the atom or molecule in the excited state, if unperturbed by the environment, is known as its natural radiative life-time.

This radiative life-time, T_N, is inversely related to the sum of spontaneous transition probabilities (ΣA_{ij}) of the molecule from all the vibrational levels of the upper state to those of the lower state obeying Franck-Condon principle, *i.e.*, it is the rate constant of spontaneous emission process. Since absorption and emission are completely reversible processes, what is probable for emission must be probable for absorption; hence life-time can be equated to the probability of absorption by the given molecule.

From the classical theory of dispersion[1-2], the transition probability is given by the oscillator strength, f, of the absorbing dipole which can be defined as the ratio of number of electrons excited to the total number of optical electrons in the system. The oscillator strength is related to the square of the transition moment integral defined by $f\psi, M\psi, d\nu$, where M is the component of dipole moment vector $\Sigma e r_i$ and r_i is the vector distance of the ith electron to the origin of a co-ordinate system fixed in the molecule, and e is the electronic charge.

Verious relations for states i and j are given as follows:

$$T = \frac{1}{\Sigma A_i} = \frac{1.5}{\nu^2_{max} \cdot \Sigma f_{ij}}$$

$$f = \frac{8\lambda^2 mc\nu}{3h} \cdot D$$

where D = dipole strength of transition $= gQ^2 = g.f\ \psi;\ \Sigma r_i \psi;\ d\nu$ which differs from the dipole moment integral by a factor 'e'. g is the multiplicity of the upper state and ν = frequency of maximum absorption in wave numbers per cm.

Dipole strength or oscillator strength is experimentally obtained from the intensity of absorption by the system. The integrated extinction coefficient $\int_{-\infty}^{+\infty} \epsilon\nu\, d\nu$, where the

integral gives the total strength for all the transitions between the two given states for frequency ranging from $+\infty$ to $-\infty$ is a better measure of intensity than the peak height at maximum absorption. The integration can be obtained from the area of the extinction curve for transition, plotted with wave number as abscissa. The final relation is

$$f = 4.32 \times 10^{-9} \int_{-\infty}^{+\infty} \epsilon_{\nu}\, d\nu$$

By considering the thermodynamic equilibrium between radiation and matter, it has been shown that there is a relationship between the probability of radiational emission from an excited state and the strength of the absorption band[3,4]. Expressing the magnitude of A_{ij} Einsteins coefficient for spontaneous emission in terms of mean life of the excited state ($1/T_N$), and B_{ij} Einsteins coefficient for induced emission by integrated absorption intensities, the value of T_N has been given by Lewis and Kasha[5] by the expression

$$T_N = \frac{3.47 \times 10^8}{\nu^2_{max}\, n^2} \cdot \frac{g_u}{g_l} \int \frac{1}{\epsilon_{\nu}\, d\nu}$$

where ν_{max} is the wave number for maximum absorption, n, the refractive index of the medium at that frequency, g_u and g_l, the multiplicities of the upper and lower states involved in the transition. For most transitions allowed by the selection rule, $g_u = g_l = 1$ (singlet→singlet), whereas for transitions involving change of multiplicity, $g_u = 3$, $g_l = 1$ (singlet→triplet). This differs from the expression given by Ladenburg only by refractive index correction term which is often taken to be unity.

These expressions are strictly true of the strength of a single atomic line where band widths are small. Under favourable conditions, the strength of a molecular transition can be obtained experimentally from and be defined by the integral of intensity over all the band lines[6]. It can be applied to complex molecules if empirical correction factors are introduced leading to the correction for the spread of the transition frequency by vibrational—electronic coupling. The calibration factor generally appears to be not more than 2 and may be even much less than this. Some values obtained by Lewis and Kasha[5] are shown in Table I, and compared with values obtained by other methods.

TABLE I

	$T_{calc.}$	$T_{obs.}$	Condition.
Rhodamin B	3.2×10^{-9}	4.2×10^{-9}	Glycerine soln. 25°.
Anthracene	2.2×10^{-8}	2.4×10^{-8}	Crystal ,,
Naphthalene	1.0×10^{-6}	0.33×10^{-6}	Crystal ,,

[The data for naphthalene were obtained by Kasha and Nauman[7].]

An improved relationship given by Forster[8]

$$\frac{1}{T_N} = 2.88\times10^{-9} \cdot n^2 \int \frac{(2\nu_0 - \nu)^3}{\nu} \cdot \epsilon\nu\, d\nu$$

where ν_0 is the wave number of approximate mirror-image reflection plane of the absorption and fluorescence spectra plotted against ν.

The main difficulties in applying this equation to spectra of complicated molecules are:

(*i*) Existence of fine vibrational peaks which introduce error in measuring the area under the absorption band.

(*ii*) Bands corresponding to the transitions of interest are overlaid by those of another electronic transitions and hence a correction for this overlap becomes necessary, which may not be easy.

(*iii*) Weak bands may "borrow" intensity from neighbouring strong bands, and may also "borrow" polarization direction.

(*iv*) Refractive index correction is still an uncertain factor.

Many recent tests for the equation have been carried out in connection with the phosphorescence of organic compounds where some of the difficulties mentioned above are absent. For singlet→triplet absorption transition, Lewis and Kasha[5] calculated the intensity of the expected absorption from the observed life-times of the phosphorescent states of a number of compounds. For phenazine, dibenzalacetone, *p*-dichlorobenzene and other compounds, the calculated band maxima were only slightly shorter than the observed phosphorescence band. Table II, based on McClure's study[9], records some quantitative comparisons of agreement between observed life-times in the triplet state and those calculated from the integrated absorption strength for $S \rightarrow T$ transitions.

TABLE II

Compounds.	Life-time (sec.) Obs.	Calc.
Benzene	7 ± 0.5	0.2 ± 1.5
Bromobenzene	0.001	0.0030 ± 0.0005
p-Dibromobenezene	0.00033 ± 0.0003	0.00153 ± 0.00006
p-Bromonaphthalene	0.021 ± 0.001	0.010 ± 0.003
p-Iodonaphthalene	0.0025 ± 0.0001	0.0019 ± 0.0001

The magnitude of natural radiative life-times provides important information regarding the "allowedness" of transition between two given states, which is governed by selection rules, symmetry properties, nature of excitation process, etc. Theory shows that the quantity $f\epsilon\nu\, d\nu$ cannot exceed 2.3×10^8 cm^{-1}, for a transition of one electron[10] and maximum value of ϵ possible for a completely allowed transition ($f = 1.0$) is about 10^5 giving natural radiative life-time equal to 10^{-9} sec. Any value less than these ideal values ($\epsilon < 10^{+5}$, $f < 1$ and $T_N > 10^{-9}$ sec.) is a measure of the forbiddenness of the transition. Fig. 1 shows relationship between these quantities together with the nature of the excitation involved [11,12].

The values of radiative life-times T_N obtained from the integrated absorption strength will give the value of natural mean life on the assumption that all the molecules excited to the higher state return to the ground state solely by radiative process. This will be then the upper limit to mean life-times. But in an actual system, specially in the condensed state, there will be other deactivating processes, which will compete with the spontaneous emission process, thereby decreasing the value for the radiational constant. After excita-

tion to the lowest singlet state, the molecule can lose its excitation energy in one or more of the following ways:

			Rate	
$A+h$	→	A^*	1.	Excitation.
A^*	→	$A+h\nu'$	α_1	Fluorescence radiation.
A^*+S	→	$A+S$ +heat	α_2	Internal conversion.
A^*+S	→	^3A+S+heat	α_3	Intersystem crossing.
A^*+M	→	$B+C$	α_4	Photochemical reaction.
A^*+A (orx)	→	$A+A$ (orx)	α_5	Non-radiative energy transfer to like molecules or foreign molecules.

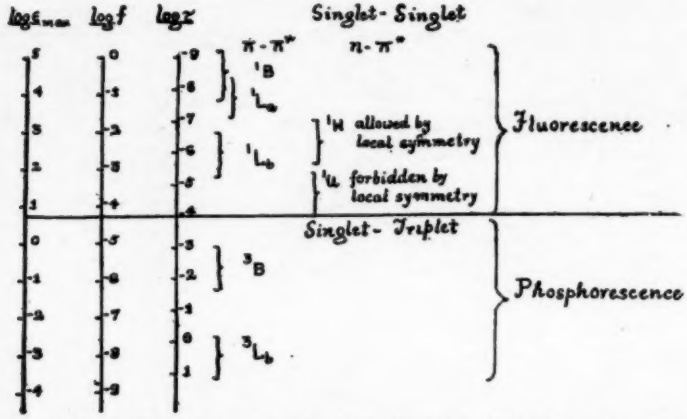

FIG. 1. The relation between natural radiative life-times (T_N), oscillator strength (f), extinction coefficient (ϵmax) of electronic transition and nature of the corresponding absorption and emission processes.

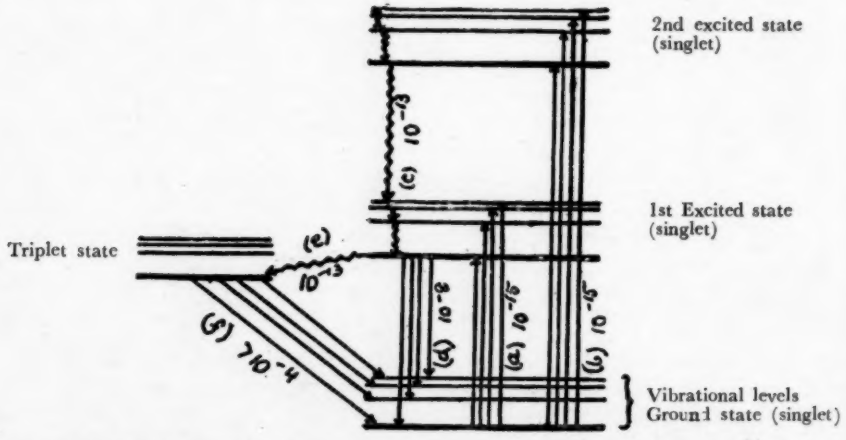

FIG. 2. Transitions and their respective time periods in sec. giving rise to absorption and emission spectra. (a) Absorption G → S , (b) G → S , (c) radiationless transition S*→S* , (d) fluorescence S* → G, (e) radiationless transition 5 → T, (f) phosphorescence T → G.

Different transitions involved are shown diagramatically in Fig. 2, where direct lines indicate radiative transitions and the wave lines, non-radiative transitions.

The natural life-time $T_N = 1/\alpha_1$ and actual lifetime $T = \dfrac{1}{\alpha_1 + \alpha_2 + \alpha_3 + \alpha_4 + \alpha_5}$

where α's are the probabilities of various processes. The life-time of the phosphorescent state T_p, will be determined by the probability of radiative intercombination with the ground state[13] after intersystem crossing from the excited singlet to triplet level (α_3). The factors which will tend to reduce T_p are (*a*) internal conversion, *i.e.*, non-radiative intercombination with the ground state, (*b*) photochemical dissociation from triplet level, (*c*) triplet→triplet radiationless energy transfer to nearby molecules[14].

Radiative transition from an excited state to the ground state is a spontaneous process; hence all photoluminescence processes follow exponential decay law. Intensity of emission at any time t, is proportional to the number (n) of molecules in the upper state and is given by the relation:

$$I = I_o e^{-kt},$$

where I_0 is the intensity when exciting source is cut off after the establishment of the photostationary equilibrium and k, the decay constant is equal to $1/T$. Putting $t = T$, we get

$$I = I_o \frac{1}{e}.$$

The life-time of an emission process is then defined as the time taken for emitted intensity I to drop to $1/e$th of its original value I_o.

"Forbiddenness" of a transition manifests itself in the emission process as increased lifetime in the excited state. Absorptions with low transition probabilities, such as symmetry forbidden or selection rule forbidden transitions, will have longer decay time. A survey of Fig. 1 shows that selection rules are more strictly followed than the symmetry condition for the two states involved in the transition. Transition with change of multiplicity is therefore less probable, giving rise to long-lived phosphorescence phenomena. A definition of fluorescence and phosphorescence can then be given as the former involves transitions between first excited singlet to ground singlet with lifetimes ranging from 10^{-9} sec. to 10^{-4} sec., and the latter involves singlet→triplet transitions with life-times 10^{-4} sec. and greater.

The direct measurement of decay period is based on the principle of permitting the observation of luminescence for a short time, which may be varied, after the end of the excitation period. Such an apparatus was first constructed by Becquerel[14]. In its simplest form, it consists of a pair of rotating sectors mounted on a common shaft, so cut that on rotation, the first admits the light beam to the sample, while the second shields the sample from the detecting device. The first sector then interrupts the source beam, and the second opens and admits light from the luminescent sample to the detector. There are several modifications of the original Becquerel phosphorescope[15]. One of its modifications[16] consists of two coaxial cylinders which can be rotated at various speeds. Outer

cylinder contains a suitable window and the inner cylinder contains the sample, solid or solution. The exciting light source and the detecting unit are placed on either side of the cylinders. During the course of rotation of cylinders, when the window faces the incident light source, the sample is excited and when in front of the detecting unit, it registers its intensity. The time between excitation and detection can be varied at will by changing the speed of rotation and complete decay curve can be plotted.

Other refinement[9] is the use of phototube as the receiving device. The signal is applied to the y-axis of the oscilloscope and phosporoscope is synchronised with the oscilloscope sweep. The oscilloscope then displays the exponential decay curve of the phosphorescence, which may be photographed. A similar method could be used with the more recently developed flash-tube techniques.

The shortest life-times that can be measured by Becquerel type phosphoroscope is 10^{-4} sec. only. For measurements of a very small decay period of the order of 10^{-9} sec., apparatuses are used, which are in principle the same as Becquerel phosphoroscope but without inertia. For this purpose, mechanical shutters are replaced by electrical devices. One of them is by using Kerr cell as superrapid time shutter. Kerr cell is a glass vessel containing highly purified nitrobenzene and two electrodes to which high voltages can be applied. The electric field causes a small degree of orientation of the liquid molecules so that the cell becomes doubly refracting like an uniaxial crystal; when it is placed in between crossed polaroids, suitably oriented, it allows the light to pass when the field is on. If rapidly oscillating voltages are applied, the cell is capable of responding by alternate transmission and extinction up to periods of 10^{-9} sec. Two such cells are used, one to admit exciting radiation and the other to pass the fluorescence from a cell of fluorescent solution. In 10^{-8} sec. light travels 300 cm. By varying the distances between the two shutters and the fluorescent substance and by proper synchronisation of the two shutters, complete decay curve can be obtained. This technique was utilized by Gaviola[17] for measurement of life-times of uranin and rhodamin and study of the effect of solvent, concentration and polarization of incident radiation. An interesting modification of Gaviola's fluorimeter was devised by Szymanowski.[18]

The Kerr cell was used to modulate the exciting light. The modulated light source, after passing through nicol prisms, was allowed to fall on a diffusedly reflecting surface. The scattered radiation is then also modulated at the same frequency as the incident radiation. If the scattering substance is now replaced by a fluorescent solution, a time lag will be introduced in the emitted radiation due to finite time between absorption and emission, which by definition is the life-time of the excited state. This time lag will introduce a phase-shift, proportional to the life-time of the emitting molecule, in the modulation frequency of the emitted radiation as compared to that from a scattering surface. Szymanowski[18] measured the ellipticities of the secondary radiations for the two processes, one for instantaneous reflection process and the other for the luminescence process, and plotted the complete curves for different positions of the two samples. The value of τ is, in first approximation, derived directly from the distance between the minima in the two curves. Decay periods as low as 10^{-9} sec. could be measured with this apparatus with an error of $\pm 0.2 \times 10^{-9}$ sec. For uranin solution, he obtained a value of 5.07×10^{-9} sec. for solutions in H_2O, EtOH and Bu^iOH, and 5.12×10^{-9} in glycerol.

In the last ten years much improvement has been made in the phase-shift method[19] which is a very accurate method for the measurement of mean life-times. Ultrasonic waves and piezo-electric crystals are used to modulate the light source. The theoretical treatment by Bailey and Rollefson[22] is given below.

The differential equation for decay in intensity of fluorescence, I, is

$$\frac{dI}{dt} = -k_1 I \qquad \ldots \quad \ldots \quad \ldots \quad (1)$$

where k_1 is considered to be the sum of all first order rate constants such as deactivation through emission and also through other processes which are first order with respect to the activated species such as interaction with the solvent molecules or quenching by specific ions in solution.

Photo-activation occurs at a rate proportional to the intensity of exciting light. When excitation is by light, varying in periodic manner, the equation becomes

$$\frac{dI}{dt} = -k_1 I + k_2 J(t) \qquad \ldots \quad \ldots \quad \ldots \quad (2)$$

where intensity of exciting light $J(t)$ may be represented as a Fourier series,

$$J(t) = \frac{a_0}{2} + \Sigma\,(a_n \cos nwt + b_n \sin nwt) \qquad \ldots \quad \ldots \quad \ldots \quad (3)$$

where $a_0/2$ indicates the average intensity of exciting light and the second term gives the periodic variation about this average; w is the circular frequency of modulation. The value of k_2 is determined by the absorption coefficient and concentration of the fluorescer and by the thickness of the solution used. In any given experiment it is constant. Substituting (3) in (2) we have

$$\frac{dI}{dt} + k_1 I = k_2 \left\{ \frac{a_0}{2} + \Sigma\,(a_n \cos nwt + b_n \sin nwt) \right\}$$

which is a linear first order equation and can be solved by usual methods giving

$$I = \frac{k_2}{k_1} \cdot \frac{a_0}{2} + k_2 \Sigma \frac{a_n (k_1 \cos nwt + nw \sin nwt)}{k_1^2 + n^2 w^2}$$

$$+ k_2 \Sigma \frac{b_n (k_1 \sin nwt + nw \cos nwt)}{k_1^2 + n^2 w^2} + C.e^{-k_1 t}.$$

By making further substitutions

$$\sin \Phi_n = \frac{nw}{(k_1^2 + n^2 w^2)^{\frac{1}{2}}}, \quad \cos \Phi_n = \frac{k_1}{(k_1^2 + n^2 w^2)^{\frac{1}{2}}}$$

$$I = \frac{k_2}{k_1} \frac{a_0}{2} + k_2 \Sigma \frac{a_n \cos (nwt - \Phi_n)}{(k_1^2 + n^2 w^2)}$$

$$+ k_2 \Sigma \frac{b_n \sin (nwt - \Phi_n)}{(k_1^2 + n^2 w^2)^{\frac{1}{2}}} + C.e^{-k_1 t} \qquad \ldots \quad \ldots \quad \ldots \quad (4)$$

Thus fluorescence intensity is represented by another Fourier series plus an additional exponential term in t. This final term, however, becomes negligibly small as t becomes large compared to $k_1\,(= 1/T)$, and can be neglected. For a given component of exciting light

a component of the same frequency is obtained in the fluorescent light, but retarded in phase by the angle Φ_n which is related to the rate constant k_1 and to the mean life-time T by the relation:

$$\tan \Phi_n = \frac{n\,w}{k_1} = nwT.$$

For sinusoidally varying light, all of the coefficients a_n and b_n for $n > 1$ are zero so that only the first component of the Fourier series remains. By proper choice of time base, either a_1 or b_1 can be made equal to zero so that exciting light is

$$J(t) = \frac{a_0}{2} + a_1 \sin wt,$$

$$I = \frac{k_2}{k_1}\,\frac{a_0}{2} + \frac{k_2}{(k_1^2 + n^2w^2)^{\frac{1}{2}}} \cdot a_1 \sin (wt - \Phi)$$

fluorescent intensity, and the phase relationship is given by $\tan\Phi = w$.

Light is modulated by a method described by Maercks[20] using ultrasonic standing waves in a liquid medium as an intermittent diffraction grating. The method of detection and measurement is similar to one suggested by Tummerman[21]

From the relationship between phase angle and life-time, it is seen that by proper choice of the frequency of modulation, the apparatus can be suited for measurement of small or large T values. Thus if two different emission processes with different life-times occur simultaneously, thees can be separated.

These authors claim an accuracy of 0.1×10^{-9} sec. for their life-time values and for the first time have shown a positive variation of mean life of fluorescein anion in alkaline solution with the concentration of the fluorescer (Table III).

TABLE III

Concentration effect on life-time of fluorescein in 0.005*M*-KOH.

Conc.	$T \times 10^9$ sec.	Conc.	$T \times 10^9$ sec.	Conc.	$T \times 10^9$ sec.
$1.6 \times 10^{-6}M$	4.6 ± 0.1	$8.0 \times 10^{-5}M$	6.5	$3.0 \times 10^{-4}M$	7.4
8.0×10^{-6}	4.6	1.0×10^{-5}	6.6	4.0×10^{-4}	7.5
1.0×10^{-5}	5.0	2.0×10^{-4}	7.0	4.0×10^{-4}	7.7
8.0×10^{-5}	6.1	2.0×10^{-4}	7.0	5.0×10^{-4}	7.9

The usual effect of increasing concentration is to decrease the lifetime due to self-quenching. This increase is explained as due to absorption—remission process within the system before an emitted quantum reaches the photomultiplier. A marked influence of secondary fluorescence has also been observed by Schmillen[22].

Further improvements in the above technique has been made by Kromman[19] (Fig. 3). A second crystal-controlled oscillator of frequency 5.2 Mcs is fed at the base of the photo-multiplier receiving an impulse of 5.0 Mcs frequency, the frequency of modulation of incident radiation. The mixing of these two frequencies produces a beat frequency of 2 Kcs. The phase-shift was observed for 2 Kcs beat frequency rather than for 5 Mcs, thereby increasing the sensitivity of detection of small phase shifts due to small life-times. The apparatus was checked by measuring the speed of light and reproducible values of 2.98×10^{10} cm per sec. were obtained.

Using this improved apparatus, (accuracy $\pm 0.5 \times 10^{-9}$), the life-times of fluoresce in

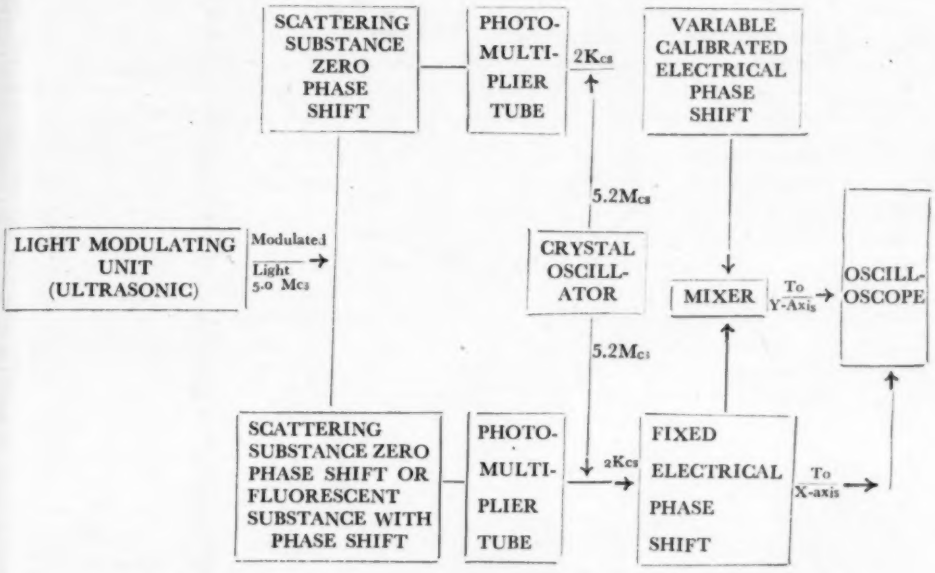

FIG. 3. Block diagram of the phase shift apparatus for the measurement of actual life-times. (Bailey & Rollefson modified by Kroman.)

in KOH was measured Rohatgi[23], in various hydroxylic solvents such as water, water-glycerol, EtOH, Pr^nOH and Bu^nOH. Whereas no difference in lifetime values for these was observed by Szymanowski[18], a decreasing order was obtained in the series EtOH, Pr^nOH, H_2O, Bu^nOH and glycerol, ranging from 6.57×10^{-9} to 6.19×10^{-9} (uncorrected for absorption-remission process). The order is the same as the boiling point of the solvents, indicating small solute-solvent interactions of van der Waal's type plus hydrogen bonding effect. Thus, this is a very good way of studying small molecular interactions in solution.

The phase-shift method is now widely used for obtaining improved values of decay periods of organic and inorganic compounds, in different states of aggregation. The values of anthracene has been obtained in vapour and in crystalline state by Galanin[24], in solution in solvent by Liebson[25] and Kroman[19], and in solid solution with tetracene and naphthacene by Schmillen *et al*[26]. An exhaustive survey of life-times of substituted aromatics, specially benzene derivatives, has been done by Dikun, Petrov and Sveshnikov[29]. Rohde[19] has also studied a number of hydrocarbons, useful in scintillation counters. Schmillen *et al.* [19,26,27] have contributed towards the life-times of various dyestuffs and studied the effect of added quenchers on their decay period. Bonch-Bruevich *et al.*[19] have measured the decay constants for colour centres in ionic crystals. Life-times of rare salts and ruby have also been measured[28].

Another important method for the measurement of decay period is from the study of depolarization of fluorescent radiation. The directional nature of light absorption implies that when a system of randomly oriented anisotropic oscillators is excited by plane polarized light, the probability of absorption will be the greatest for those molecules which are

oriented with their chromophoric group parallel to the electric vector of the incident radiation. Other molecules will have smaller probability given by $A = A_{max}\cos^2 \alpha$, where A_{max} is the maximum probability of absorption for parallel orientation and α, angle between the vector direction and the chromophoric group. When $\alpha = 90^\circ$, *i.e.* for perpendicular orientation of the chromophore, the absorption probability is zero.

If the molecules do not rotate during the period between absorption and emission processes, *i.e.*, if the molecules are embedded in a medium of infinite viscosity, the electric vector of emitted radiation will have the same orientation as the emitting oscillator. Since there are molecules of all orientation, the degree of polarization of emitted radiation will be much reduced. For a randomly oriented molecule in a medium of infinite viscosity, when observed at right angles to the direction of incidence, the intensity of emitted radiation with electric vector parallel to incident vector (I_{11}) is three times the intensity with emitted vector perpendicular to incident vector (I_1). The degree of polarization p, is then given by (Bowen and Wokes[193])

$$p = \frac{\Phi\, I_{11} - I_1}{I_{11} + I_1} = 0.5.$$

Therefore, the maximum value for p in a system with all orientations is 50%. This maximum value will not be observed in liquid solvents where the molecule has the possibility of rotation (time period 10^{-11} sec.) within the life-time of the excited molecule ($T = 10^{-8}$ secs.). But in viscous solvents like glycerol and ethylene glycol, the rotation of the molecule will be impeded to different degrees in proportion to the viscosity of the solvent. The extent of rotation within the life-time of the molecule will manifest itself in further depolarization of emitted radiation from its ideal value of 50%.

According to the theory developed by Smoluchowski[30] and by Einstein[31], considering the Brownian movement of rotation, a spherical particle of volume V, rotates in a liquid of viscosity η in a short time $\triangle t$ through an angle α. The mean value of this angle of rotation is given by

$$\triangle \alpha^{-2} = \frac{1}{3}\frac{RT}{\eta V}\triangle^{-}t$$

By inserting sufficiently short life-time T for $\triangle t$ in the above equation, an expression was derived by Perrin[32] and others[35], giving the reduced degree of polarisation which results from rotation of all individual resonators around statistically oriented axes, as

$$p = P_o \frac{1}{1 + (1 - \frac{1}{3}p_o)\frac{RT}{\eta V}T}$$

where P_o is maximum polarizability at infinite viscosity and R and T have their usual significance. Molar volume of the solution, V, can be obtained from Einstein's equation

$$\frac{\eta' - \eta}{\eta} = \frac{5}{2} \cdot \frac{C}{M} \cdot V$$

where η' is the viscosity of solution of conc. C g./c.c. of a substance of molecular weight M in a solvent of viscosity η. Hence V will vary from solvent to solvent.

The equation can be written as

$$\frac{1}{p} = \frac{1}{P_o} + \left(\frac{1}{P_o} - \frac{1}{3}\right)\frac{RT}{V}\tau$$

showing a linear relationship between $1/p$ and $1/\eta$.

If degree of polarization is measured in a number of solvents of varying viscosity, the intercept of $1/p$ against $1/\eta$ plot will give the value of $1P/_o$, and from the known values of pT/V life-time τ can be calculated from the slope. The viscosity can be varied by mixing two solvents of different viscosity in different proportions, using a series of homologous compounds, by using polymerizable solvents or by changing the temperature. In the last case, not only the variation of η but that of τ also should be taken into account[35]. The viscosity is found to have a greater effect on polarization than temperature[36]. The expression has been well verified by experimental studies on polarized fluorescence of dyes, hydrocarbons, cyanoplatinites and uranyl salts in liquid solutions.

From general considerations of the theory, it is expected that the observed degree of polarization will depend on the life-time of the molecule. If the life-time is short, polarization will be greater than for substances of longer life-times. For example, an aqueous solution of erythrosin shows strong polarization ($\tau \approx 10^{-9}$ sec.), whereas the fluorescence of uranyl salts is completely depolarized ($\tau \approx 10^{-6}$ sec.). In partially quenched solutions, the degree of polarization increases as the life-times are shortened[37,38].

In order to derive correct values from this expression, plausible values of $\bar{V}$ must be introduced. This value may change from solvent to solvent since it is not the volume of isolated solute molecule but the volume of molecule with its solvation envelop. Therefore, $1/p$ should be plotted against $1/\eta\bar{V}$ to give correct results[39]. The value of $\bar{V}$ was obtained by Perrin from diffusion coefficient. The values of P_o and τ, calculated by him, are given in Table IV.

TABLE IV

	Fluorescent compounds						
	Uranin.	Erythrosin.	Resorufin.	Chlorophyll.	Quinine sulphate.	Anthracene.	Cyanoplatinite.
P_o	44	45	44	43	46	25	40
$\tau \times 10^9$	4.3	0.08	3.1	30	40	250	0.3

Furthermore, it is not always clear that the macro-and micro-viscosities are the same. Even in a very viscous solvent, molecule may have the freedom to rotate so that the value of V, obtained from diffusion coefficient data and the apparent viscosity, may give erroneous results[40]. The fluorescence of uranin and rhodamin in an ether-collodion solution is depolarized to nearly the same extent as in pure ether solution[41]. On the other hand, solutions in 90% ordinary gelatine and those in β-gelatine show large polarization although the difference in viscosity of the two solutions is thousandfold. The important property is apparently not the viscosity of the solution, but the mobility of the molecules to which the dye is attached or on which it is adsorbed[42].

Perrin's expression has been derived on the assumption that $\mathcal{T}$ is independent of of viscosity. If $\mathcal{T}$ is a function of η, the equation cannot be applied[42]. Besides, the value of $\mathcal{T}$ may not be the same in different solvents employed to vary the viscosity. In such cases, relative quantum yield (Q_r) also becomes a variable and Q_r should be plotted against $Tr/\eta V$.

The degree of polarization must be measured at very low concentrations, because in concentrated solutions resonance-energy transfers of excitational energy between oscillators of different orientations will also lead to additional depolarization[45].

Tawde and Ramnathan[44] have shown an increase in mean life-times with increasing concentration of dyestuffs like Safranin T, Acridine Orange R., etc. These are expected to decrease again after a certain critical concentration[45].

There are some important methods for the determination of life-times of excited states of fluorescent molecules. It may be mentioned here that these life-times are for the first excited singlet (fluorescent) or lowest triplet (phosphorescent) state of the molecule only, because only these two are the emitting states. One exception is the case of azulene[46], where emission takes place from the second excited state. In general, molecules excited to higher states lose their energy by vibrational cascade and emit only from the first singlet state. So we can say that life-times of higher states are only 10^{-13} sec. or less. (Fig. 2).

It should be interesting to compare the data obtained from all these different methods. The values obtained from integrated absorption strength is although expected to give the ideal life-times $\mathcal{T}_N$, there are certain uncertain factors in the calculation, such as correction for refractive index, band width, intensity borrowing, etc. Relative values should be pretty good by this method. The values from phase-shift method need corrections for various quenching effects and for errors due to overlap of absorption and emission spectra. A comparison of the values obtained from these two methods in conjunction with known values of photoluminescence efficiencies give deep insight into the nature of radiationless processes[47].

The measurement of fluorescence efficiency under conditions of equal light absorption can be related to life-times by $I_1/I_2 = \mathcal{T}_1/\mathcal{T}_2$. Therefore, life-times can be calculated from the quenching data[48], if the sphere of action of quenching collison can be estimated. Such an estimate is possible if one can measure the quenching and polarization in the same medium under the same conditions since the latter is influenced by the rotating Brownian motion which can only be obtained from the kinetic dimensions of the molecule. Recently Jablonski[49] has made a fresh approach to derive expressions to describe decay of photoluminescence and its dependence on polarization for molecules distributed according to the Smoluchowski distribution. A comparative study of $\mathcal{T}$ by different methods can reveal interesting information regarding the nature of luminescence phenomena and mechanism of its inhibition. Whether $\mathcal{T}$ depends on the physical state of the molecules is still a controversial question[50]. In this review, stress has been given mainly on the condensed system. Importance of life-time data is increasing because of increasing use of fluorescent substances as scintillation counters and in other industrial and theoretical applications. Fluorescent compounds may show different characteristics under high energy excitation[51]. An exhaustive review of properties of fluorescent compounds used as scintillators is given by Sangster *et al*[52].

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Fatty Acid Derivatives of Aluminium, Titanium, and Zirconium

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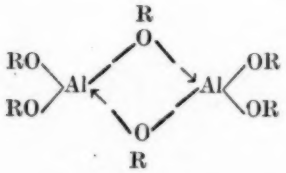
The existence of tri-, di-, and mono-soaps of aluminium has been in question for a long time. Conflicting opinions have been expressed regarding formation of all the three types. The publications of McBain and McLatchie[1] and others[2-6] over the last two decades pointed towards the non-existence of definite carboxylates of aluminium. As opposed to this, the only evidence pointing towards possible existence of tri-soaps of aluminium are (*i*) the observation of Lawrence[7] showing that three moles of alcohol can be distilled by a reaction between aluminium alkoxides and excess of fatty acids, and (*ii*) the synthesis of aluminium trilaurate by Glazer *et al.*[8] Not only was the existence of tri-derivatives doubted, but the formation of even the mono- and di-soaps of aluminium was not fully established. The position has been summarised in a recent publication by Alexander[9] in the following words: "On the basis of synthetic and analytical data, obtained from the experiments in non-aqueous media, there is no evidence for the existence of mono- and tri-soaps of aluminium. Aluminium di-soaps of the type $Al(OR)F_2$ and $Al(OH)F_2$ can be prepared ".

Detailed investigations regarding the preparation and properties of aluminium alkoxides[10] has revealed the extraordinary strength of the bridge structure of the following type:



On the basis of the above, the observation that only two moles of the corresponding alcohol can be distilled easily when aluminium ethoxide or isopropoxide is treated with an excess of either a tertiary alcohol itself[10] or its ester[11], can be easily explained. Similar observations were made on treating aluminium isopropoxide with three moles of a fatty acid[12]. On fractionating the alcohol produced azeotropically with benzene, two moles of the alcohol could be distilled with facility. The replacement of the third alkoxy group, although slow, did, however, occur at a measurable rate and finally all the three moles of alcohol per mole of the alkoxide could be distilled off. The product was found to be stable to heat (up to a temperature of about 200°) under reduced pressure (0.1 mm) and showed an analysis corresponding closely with aluminium tri-soaps. To substantiate the work fully, aluminium isopropoxide was treated with an excess of fatty acids[13] and after removing the full amount of alcohol (found experimentally to be 3 moles per mole of the alkoxide in each

case) azeotropically, the excess fatty acid was removed either (*i*) by extracting the excess fatty acid with a suitable solvent like acetone or dioxane from the insoluble tri-soap, or (*ii*) by distilling the excess fatty acid (in the case of lower fatty acids) under reduced pressure. Tri-derivatives of aluminium with fatty acids (from acetic to stearic acid) have been synthesised and characterised in this manner. The work has been confirmed in a later publication by Gilmour *et al.*[14] by X-ray analysis and also by Schaeffer and coworkers[15] by infrared studies.

Following the above work, it has been further found[16] that mono- and di-alkoxy carboxylates can be prepared by metathetic reaction between aluminium isopropoxide and the calculated amount of the corresponding fatty acid. These alkoxy carboxylates yield the corresponding chloride alkoxides on treatment with acetyl chloride. It has been further shown[17] that the tri-carboxylates of aluminium can also be prepared by the reaction between aluminium isopropoxide and acid anhydrides:

$$Al(OPr^i)_3 + 3\begin{matrix}RCOO\\RCOO\end{matrix}\!\!>\!O \rightarrow Al(RCOO)_3 + 3\ RCOOPr^i$$

Further work in these laboratories[18] has shown that aluminium chloride carboxylates can be produced by stepwise reactions:

$$AlCl_3 + RCOOH \rightarrow AlCl_2(RCOO) + HCl$$

$$AlCl_2(RCOO) + RCOOH \rightarrow AlCl(RCOO)_2 + HCl$$

$$AlCl(RCOO)_2 + RCOOH \rightarrow Al(RCOO)_3 + HCl$$

Ebullioscopic measurements of molecular weights of tri-soaps in benzene have shown them to be molecularly dispersed, throwing doubt on the structures suggested recently by Schaeffer *et al*[15].

In view of the high susceptibility to moisture and hydrolysis of the three above types of carboxylate derivatives, rigorously controlled conditions are required before reproducible data on the physical properties can be obtained. Preliminary work, however, appears to lend support to the gelation theory of Schulman *et al*[19]. Tri-soaps and the mono- and di-alkoxy as well as chloro-soaps of aluminium have been found to provide mobile solutions of low viscosity in hydrocarbon solvents, with a strong tendency of forming stable gels as soon as the derivatives are exposed to hydrolysis. Detailed work on the rate and extent of gelation and on other physical properties like conductivity and dielectric constants is under progress.

In view of the increasing interest in the chemistry of titanium and zirconium, it was thought worthwhile to extend the above work to the carboxylates of these metals also. Compared to the vast literature about aluminium soaps, very little work seems to have been done on the soaps of titanium. Plechner *et al.*[20] described the preparation of titanium tetra-soaps by reacting titanium tetrachloride with fatty acids in presence of calcium carbonate.

$$TiCl_4 + 4RCOOH + 2CaCO_3 \rightarrow Ti(RCOO)_4 + 2CaCl_2 + 2H_2O + 2CO_2.$$

Repeated attempts to prepare the tetra-soaps by the above reaction always resulted in hydrolysed products, which was not surprising in view of the side formation of water in

the reaction itself[21]. Following the success achieved in the preparation of aluminium tri-soap sthe corresponding reaction between titanium alkoxides and fatty acids was tried[22] for the preparation of tetra-soaps of titanium.

$$Ti(OR)_4 + 4R'COOH \longrightarrow Ti(OOCR')_4 + 4\ ROH$$

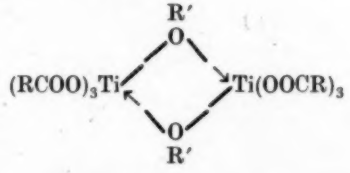
In the above reaction only three moles (approximately) of the alcohol could, however, be distilled even when an excess of the fatty acid was present. Table I records the results obtained in some of the attempts on the above mentioned lines.

TABLE I

Reactions of titanium alkoxides with varying excess of different fatty acids.

Fatty acids.	Alkoxides.	Molar ratio of alkoxide to acid.	Moles of corresponding alcohol replaced per mole of alkoxide.
Acetic	$Ti(OPr^i)_4$	1 : 5.0	2.9
Propionic	$Ti(OPr^i)_4$	1 : 5.9	2.9
Butyric^n	$Ti(OPr^i)_4$	1 : 6.1	3.0
Valeric^n	$Ti(OEt)_4$	1 : 4.4	2.7
Lauric	$Ti(OEt)_4$	1 : 4.4	2.8
Myristic	$Ti(OEt)_4$	1 : 4.37	2.9
Palmitic	$Ti(OPr^i)_4$	1 : 4.6	2.8
Palmitic	$Ti(OEt)_4$	1 : 4.1	2.8
Stearic	$Ti(OPr^i)_4$	1 : 4.0	2.9
Stearic	$Ti(OEt)_4$	1 : 3.0	2.9
Stearic	$Ti(OBu^n)_4$	1 : 5.1	2.8

The non-replacement of the fourth alkoxy group in these reactions could be explained on the basis of steric hindrance, as already described in the case of aluminium and zirconium alkoxides[23]. Titanium alkoxides, like their aluminium and zirconium analogues, have been shown to be polymerized[24] and hence based on the structures assigned to these compounds by Caughlan *et al.*[25] The associated nature of mono-alkoxy tri-soaps of titanium could possibly involve a bridge structure of the type:



In such a structure, the titanium atoms may be so sterically surrounded that the co-ordination of another fatty acid molecule becomes impossible and hence no further replacement of the alcohol could be achieved.

To test the above explanation, attempts were made to replace the remaining alcohol in the above reaction products with higher alkoxy groups by the well known interchange reactions or with hydroxy groups by treatment with wet benzene. In neither case could an appreciable amount of the alcohol be distilled. In this connection, it may be worth

mentioning that the fourth butoxy group was difficult to be replaced when titanium butoxide was hydrolysed[26]; an extensive hydrolysis of titanium ethoxide[27] was found to result finally in a product of the type, $Ti_2O_3(OEt)_2$.

In order to determine the nature of the end products in the reactions between titanium alkoxides and excess fatty acids, the remaining fatty acid in the product was removed either (*i*) by extracting with a suitable solvent like acetone, or (*ii*) by heating the product under reduced pressure. On analysing the products after being submitted to the above treatments, the analysis was found to correspond with titanium derivatives of the type $TiO_x(RCOO)_{4-2x}$ with the value of x nearly 0.5. At the same time analysis of the acetone-soluble portion showed it to be a mixture of the fatty acid and its ester (RCOOR′+RCOOH).

The solvent extraction experiments threw fresh light on the above acidolysis reactions, showing that the reaction between titanium alkoxides and fatty acids was not straightforward as in the case of analogous reaction with aluminium alkoxides. At some stage in the above acidolysis experiments, side reactions begin to take place resulting in the formation of organic esters and basic titanium soaps. In order to determine the stage at which complicating side reactions began to take place, titanium alkoxides were first treated with two moles of fatty acids.

$$Ti(OR)_4 + 2R'COOH \longrightarrow Ti(OR)_2(OOCR')_2 + 2ROH$$

It was found that two moles of alcohol could be replaced within a short time. The products on analysis were found to be pure titanium di-soaps of the type, $Ti(OR)_2(OOCR')_2$, indicating the existence of titanium di-soaps as definite chemical entities. Further, the above di-soaps interchanged their alkoxy content with higher alcohols[28] by carrying out the reaction in presence of benzene:

$$Ti(OR)_2(OOCR') + 2Bu^nOH \longrightarrow Ti(OBu^n)_2(OOCR')_2 + 2ROH.$$

When the above di-alkoxy di-soaps of titanium were treated with further amount of fatty acid, complicated side reactions began to take place with the formation of organic ester. The following mechanism (which fits very well with all observed facts) was therefore suggested:

$$Ti(OR)_2(OOCR')_2 + R'COOH \longrightarrow Ti(OR)(OOCR')_3 + ROH \quad \ldots\ldots\ldots\ldots\ldots\ldots (i)$$

$$Ti(OR)(OOCR')_3 \longrightarrow TiO(OOCR')_2 + R'COOR \quad \ldots\ldots\ldots\ldots\ldots\ldots (ii)$$

$$Ti(OR)(OOCR')_3 + Ti(OR)_2(OOCR')_2 \longrightarrow O\begin{matrix}Ti(OOCR')_2\\ Ti(OR)(OOCR')_2\end{matrix} + R'COOR \quad \ldots\ldots\ldots\ldots\ldots\ldots (iii)$$

Compared to (*iii*) the decomposition reaction (*ii*) appeared to increase as the carbon chain in the fatty acid increases in length. The overall reaction can therefore be represented as:

$$Ti(OR)_2(OOCR')_2 + R'COOH \longrightarrow TiO(OOCR')_2 + O\begin{matrix}Ti(OR)(OOCR')_2\\ Ti(OR)(OOCR')_2\end{matrix} + R'COOR + ROH$$

After having studied in detail the reaction of titanium alkoxides and fatty acids[29], the reaction of titanium alkoxides with acetic anhydride was studied[30].

Titanium alkoxides were treated both in the presence and absence of an inert medium (benzene) with excess acetic anhydride when the following reaction could be expected to take place:

$$Ti(OR)_4 + 4Ac_2O \longrightarrow Ti(OAc)_4 + 4AcOR$$

In no case could a tetra-acetate be obtained and the analysis always corresponded to an oxygen bridge product of the type, $O\begin{<}Ti(OAc)_3 \\ Ti(OAc)_3\end{>}$

To investigate the matter further, the reactions of titanium isopropoxide with acetic anhydride (in the molar ratio of 1:1, 1:2 and 1:3) were tried. In the first two cases, the reaction was highly exothermic, facile and resulted in the formation of pure mono- and di-acetate derivatives:

$$Ti(OPr^i)_4 + Ac_2O \longrightarrow Ti(OPr^i)_3(OAc) + AcOPr^i$$

$$Ti(OPr^i)_4 + 2Ac_2O \longrightarrow Ti(OPr^i)_2(OAc)_2 + 2AcOPr^i.$$

The reaction of titanium isopropoxide with three moles of acetic anhydride, however, always resulted finally in the formation of a product which corresponded in analysis to

$$O\begin{<}Ti(OPr^i)(OAc)_2 \\ Ti(OPr^i)(OAc)_2\end{>},$$

indicating that after the formation of the di-acetate derivative, the reaction became complicated. The above product on treatment with further acetic anhydride yielded the basic tri-acetate.

The above facts can be explained on the following simple mechanism:

$$Ti(OR)_2(OAc)_2 + Ac_2O \longrightarrow Ti(OPr^i)(OAc)_3 + AcOPr^i$$

$$Ti(OPr^i)(OAc)_3 + Ti(OPr^i)_2(OAc)_2 \longrightarrow O\begin{<}Ti(OPr^i)(OAc)_2 \\ Ti(OPr^i)(OAc)_2\end{>} + AcOPr^i$$

Further, the above study has been extended to the reaction of titanium tetrachloride and fatty acids[31]. These reactions were found to be even more complicated than the corresponding reactions of fatty acids with titanium tetra-alkoxides. Very long period (up to 100 hours) of refluxing in benzene were required before the hydrogen chloride could be driven out of the reaction mixture. Also, the titanium chloride appeared to catalyse some side-condensation reactions (cf. catalytic power of aluminium chloride for a large variety of organic reactions). Therefore, to elucidate the nature of the above complicated reaction, the lowest member of the fatty acid series, acetic acid was chosen. In this case also, the reaction has been observed to be simple and straightforward up to the formation of titanium dichloride di-acetate. With the interaction of the third mole of acetic acid and the formation of titanium monochloride tri-acetate, decomposition, however, begins to take

place, finally resulting in the formation of a mixture of basic di- and mono- acetate of the type:

$$TiO(OAc)_2 \text{ and } O\begin{<}Ti(OAc)_3 \\ Ti(OAc)_3\end{>}$$

It has been therefore referred that the reaction of fatty acids with titanium tetrachloride is similar to that with titanium alkoxides.

Finally, the reaction of titanium tetrachloride with acetic anhydride was attempted with a view to preparing the tetra-acetate. Results similar to the above, however, were obtained and the final product was always found to correspond in analysis to a basic tri-acetate:

$$O\begin{<}Ti(OAc)_3 \\ Ti(OAc)_3\end{>}$$

Thus the treatment of the tetra-derivatives of titanium, $TiCl_4$ or $Ti(OR)_4$, with acetic acid-anhydride mixture always results in a basic tri-acetate. Further, it was found that treatment of hydrolysed titanium alkoxides or tetrachloride (or even hydrated titanium dioxide) with acetic anhydride yields the same basic tri-acetate product.[32]

$$O\begin{<}Ti(OAc)_3 \\ Ti(OAc)_3\end{>}$$

TABLE II

No.	Reactions.	Analysis of the product. Found.		Calc. for $O\begin{<}Ti(OAc)_3 \\ Ti(OAc)_3\end{>}$	
		%Ti.	%OAc.	%Ti.	%OAc.
1.	$Ti(OPr^i)_4+Ac_2O$	20.55	76.3		
2.	$Ti(OEt)_4+Ac_2O$	20.62	76.5		
3.	$TiCl_4+Ac_2O+AcOH$	20.56	78.2	20.55	76.0
4.	Hydrolysed $Ti(OPr^i)_4+Ac_2O$	20.40	76.5		
5.	$Ti(OH)_4+Ac_2O$	21.20	75.8		

Thus it appears that the basic tri-acetate is always the end product, whether we treat titanium tetra-derivative (like tetra-alkoxide or tetrachloride) or more hydrolysed titanium derivatives, with acetic anhydride or a mixture of acetic acid and acetic anhydride.

Zirconium isopropoxide and excess of a fatty acid (stearic, palmitic, lauric and caproic) yield basic tricarboxylates[33], $(R.CO_2)_3\ Zr.O.Zr(CO_2R)_3$, which remain unchanged on repeated crystallisation from dioxan. The reaction was carried out in refluxing benzene under a column so that the isopropyl alcohol produced could be removed azeotropically with benzene. The alcohol in the azeotrope was estimated. Even when the ratio zirconium isopro-

poxide: fatty acid was more than 1:4, not more than 4.5 moles of alcohol per mole of the crystalline isopropoxide $Zr(OPr^i)_4,Pr^iOH$ distilled azeotropically. It thus appeared that the replacement of the fifth alcoholic group might be slow owing to steric hindrance, or that a side reaction occurred owing to which a portion of the replaceable alcohol in the alkoxide could not be distilled. For example, the fact that 4.5 moles of alcohol are replaced can be explained simply if the main reaction is represented as:

$$2[Zr(OPr^i)_4,\ Pr^iOH]+6R.CO_2H \longrightarrow 2Zr(OPr^i)(R.CO_2)_3+8Pr^iOH \quad \ldots \quad \ldots \quad (i)$$

$$Zr(OPr^i)(R.CO_2)_3+R.CO_2H \longrightarrow Zr(R.CO_2)_4+Pr^iOH \text{ (slow)} \quad \ldots \quad \ldots \quad (ii)$$

$$Zr(OPr^i)(R.CO_2)_3+Zr(R.CO_2)_4 \longrightarrow (R.CO_2)_3Zr.O.Zr(CO_2R)_3+R.CO_2Pr^i \quad \ldots \quad (iii)$$

The reaction of zirconium tetra-isopropoxide with palmitic and stearic acids was carried out stepwise:

$$Zr(OPr^i)_4,Pr^iOH+R.CO_2H \longrightarrow Zr(R.CO_2)(OPr^i)_3+2Pr^iOH \quad \ldots \quad \ldots \quad \ldots \quad (iv)$$

$$Zr(OPr^i)_4,Pr^iOH+2R.CO_2H \longrightarrow Zr(R.CO_2)_2(OPr^i)_2+Pr^iOH \quad \ldots \quad \ldots \quad (v)$$

These replacements were rapid and the benzene—isopropyl alcohol azeotrope distilled quickly. Tri-isopropoxyzirconium monostearate and monopalmitate and diisopropoxyzirconium distearate and dipalmitate were isolated in pure states. These are stable to heat under reduced pressure, but are susceptible to atmospheric moisture.

The di-soaps were treated with fatty acids (palmitic or stearic) in the molar ratio 1:1. On fractionation almost 1 mole of alcohol distilled azeotropically, indicating the simple reaction:

$$Zr(OPr^i)_2(R.CO_2)_2+R.CO_2H \longrightarrow Zr(OPr^i)(R.CO_2)_3+Pr^iOH \quad \ldots \quad \ldots \quad \ldots \quad (vi)$$

From the remaining solution, benzene was distilled off under reduced pressure and the solid products were analysed. The zirconium content corresponded to the monoisopropoxy tricarboxylate, but the isopropoxy content was considerably below theoretical. Further, the isopropoxy content depended on the amount of heating to which the products were subjected. If the monoisopropoxy tristearate decomposes:

$$Zr(OPr^i)(R.CO_2)_3 \longrightarrow O:Zr(R.CO_2)_2+R.CO_2Pr^i \quad \ldots \quad \ldots \quad \ldots \quad \ldots \quad \ldots \quad (vii)$$

the analytical results could be explained. The product from reaction (vi) was treated with dry dioxan; the crystallised zirconium soap on analysis corresponded to a mixture of $ZrO(R.CO_2)_2$ and $Zr(OPr^i)(R.CO_2)_3$. The sweet-smelling dioxan-soluble portion was a mixture of the fatty acid and ester; on analysis a sample conformed with the decomposition (vii).

The isolation of the isopropoxyzirconium tristearate is therefore only possible by carrying out the reaction at a low temperature:

$$Zr(OPr^i)_4+3R.CO_2H \longrightarrow Zr(OPr^i)(R.CO_2)_3+3Pr^iOH \quad \ldots \quad \ldots \quad \ldots \quad \ldots \quad (viii)$$

The correctness of the overall reaction mechanism (iii) has been further demonstrat-

ed[34] by refluxing an equimolecular mixture of the isopropoxyzirconium tristearate and the tetrastearate, whereupon the reaction (ix) takes place:

$$Zr(OPri)(stearate)_3 + Zr(stearate)_4 \longrightarrow O\begin{matrix}Zr(stearate)_3\\ Zr(stearate)_3\end{matrix} + Pr^i(stearate) \quad \ldots\ldots\ldots\ldots (ix)$$

Having failed to prepare zirconium tetra-soaps by the above reaction, we tried to make zirconium tetrachloride react with fatty acids (stearic, palmitic, and myristic). Although the tetrachloride is not appreciably soluble in benzene, it slowly reacted with fatty acids when refluxed and hydrogen chloride evolved freely. Refluxing was continued until evolution of hydrogen chloride became negligible, when the solution gave colorless crystals of tetra-soaps:

$$ZrCl_4 + 4R.CO_2H \longrightarrow Zr(R.CO_2)_4 + 4HCl \quad \ldots\ldots\ldots\ldots (x)$$

Repeated crystallisation from benzene did not noticeably change the analysis of the product whose identity is thus confirmed.

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Development of Plant Chemistry in the Indian Sub-continent

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The use of crude plant extracts in therapy was known in India in the remote past. There is ample proof of applications of various recipes of Indian herbs in curing many a malady and realisation of herbal charms led to the development of Ayurvedic system of medicine. The latter comprises an important part of *Atharva Veda*, the most ancient treatise of Hindu medicine (1000 B.C.), viz., *Charak* and *Susruta Samhita* (written not later than 300-200 B.C.), which constitute two important sections of Ayurveda and deal with drug plants of ancient India. These volumes are considered to be monumental works towards our knowledge of science and art of healing.

From the Vedic period down to the Mohammedan invasion of India, Hindu medicine made a remarkable progress and permeated into Egypt, Greece and Rome, Arabia and Persia. This phytotherapy further flourished during the reign of Ashoke the Great, when many exotic plants were naturalised in this country (274-232 B.C.). The Emperor Ashoke sent the Buddhist monks to remote parts of the world to preach Buddhism. They carried medicinal plants with them for their own use and on their way back to India collected many new plants. These botanical specimens have now been naturalised, thus enriching the Indian flora.

Foreign influence on the study of Indian plants dates back to the 16th century when Portugese and Dutch scientists came to India. They took interest in the study of vegetable drugs and published many books of which "Hortus Malabaricus" written by Van Rheedes in 12 volumes (A.D. 1678-1703) is a valuable contribution.

With the advent of Western therapy in this country, glories of Ayurvedic medicine rapidly declined. It was later realised that Indigenous system of therapy should be revived from economic consideration. In the early part of the nineteenth century, a great campaign was started for restoring the old system of Ayurvedic medicine. William Jones, John Flemming, W. Roxburgh and W. Ainslie and others were active participants. They published several books on "Medicinal Herbs" of India and could make the people understand that India with variabilities of climate is a rich nursery in the world botany and this nursery is a big store-house of medicine. Thus, the importance of phytochemistry was recognised by Eastern as well as by Western scholars. But it was not possible to carry on research on Plant Chemistry on sound scientific basis till the end of the last century when scientific methods and techniques became available to the investigators[1].

The first chemist to investigate plant products in India was W. O. Shaugnessy (1840) of Calcutta Medical College. Studies on medicinal and poisonous plants of India were later undertaken with right earnest in the same Institution by Warden and Hooper and they were the first to isolate arbin and a toxic protein, the poisonous principles of *Arbus preca-*

torius (kunch). These workers compiled an authoritative book on Indian drugs, 'Pharmacographia Indica', in collaboration with W. Dymock (1890-1899). Simultaneously many other important books appeared, of which the following ones are worthy of mention:

(*a*) Materia Medica of the Hindus by U. C. Dutta (1870).
(*b*) A Dictionary of the Economic Products of India by George Watt (1889-1893).
(*c*) Indigenous Drugs of India by K. L. Dey (1896).
(*d*) Indian Medicinal Plants, Vols. I and II by K. R. Kirtikar and B. D. Basu (1918).

In 1896, E. J. Hill[2] in Allahabad isolated the colouring matter of *Nyctanthes arbortristis* Linn. and studied its properties. During the period 1912-1924, much interest was shown on phytochemistry[3], and valuable research was carried out at Bangalore, Madras, Forest Research Institute (at Dehra Dun), Dacca, and Calcutta, etc., —notable workers[2] being J. L. Simonsen, E. R. Watson, J. J. Sudborough and their brilliant Indian collaborators. Simonsen (1910-1927) (in Bangalore and Forest Research Institute, Dehra Dun) carried intensive work on various essential oils isolated from a large number of *Gramineae, Coniferae* and *Compositae* species and elucidated the structures of santalene (the red colouring matter of Sandal Wood), myrcene, *d*-α-phellandrene, $\triangle^3$-and $\triangle^4$-carenes, *d*-piperitol, *d*-piperitone, *l*-carvomenthone, *d*-α-thujene, *l*-sabinene, zingiberine, curcumene, and longifolene, etc. He also established the structure of morindone and studied the composition of various seed oils from indigenous sources.

In Dacca, E. R. Watson (1910-1924) and his school published papers on seed oils and on the odorous and bitter constituents of neem oil. He also investigated the preparation of camphor from pinene and determined the pinene content of Indian turpentine oils. Watson studied the strychnine and brucine content of the seeds of Nux-vomica (*Strychnos nuxvomica* Linn).

J. J. Sudborough (1916-1927) examined a large number of essential and fatty oils from a wide variety of sources and established a relationship between the refractive index and the iodine value of a number of fatty oils from Indian plants. Sudborough and his co-workers investigated the production of caffeine from tea waste.

The Forest Research Institute at Dehra Dun did valuable work on timbers.

Under the auspices of the Lac Research Institute at Ranchi and under the guidance of G. J. Fowler (1915-1924) at Bangalore, a large number of workers studied the chemical composition of Lac and Shellac and helped to a great extent the industrial development in this field.

In the second quarter of this century, proper collaboration between botanists, chemists and pharmacologists was rendered possible for the first time and arrangements for clinical trials of the drugs were made by the establishment of a research hospital. This gave a great impetus to the development of phytochemistry and intensive research on the chemistry and pharmacology of plant products started in various parts of India in the following main channels:

1. Indian plants which have been recognised by the pharmacopoeias of various advanced countries as well as those which are being cultivated in this country.
2. Substitutes for pharmacopoeial drugs.
3. Plants used in the Indian indigenous system of medicine.
4. Poisonous plants.
5. Aromatic plants.

In the past two decades the research work on phytochemistry has received considerable encouragement through generous grants from the Council of Scientific and Industrial Research, the Indian Council of Medical Research, the Indian Council of Agricultural Research, the University Grants Commission, the National Institute of Sciences of India, the Universities and pharmaceutical concerns. With the development of physicochemical methods, e.g., column chromatography, paper chromatography, counter-current method, ultraviolet, infrared, and nuclear magnetic resonance spectroscopy, X-ray crystallography, mass spectrometry, and their applications in structural elucidation of organic compounds together with the spectacular advancement of knowledge on the biogenesis of natural products enriched by tracer technique, phytochemistry is making rapid and tremendous progress.

There is a great tendency in recent years among chemists to undertake this kind of work and much useful data on the chemical and pharmacological properties of the active principles of indigenous drugs have been furnished by many phytochemists in India. The C. S. I. R. has set up a Central Indian Medicinal Plant Organization and the Government of West Bengal has also organized a Medicinal Plants Committee of which Hon'ble Dr. B. C. Roy, the Chief Minister of West Bengal is the Chairman and under the direction of the Chairman and the Committee, cultivation of many important plants e.g., *Cephaoelis ipecacuanha* Brot., *Ergot* (*Claviceps purpurea*), *Rauwolfia canescens* Linn., *Rauwolfia serpentina* Benth., *Mentha* (arvensis) species, etc., has already been started. A plant survey in Eastern, Western, and Southern zones is being made by the Botanical Survey of India to collect a complete list of Indian flora for their studies on modern scientific lines with a view to making the country self-supporting by enabling her to utilize drug plants produced in the country. On the whole, it may be said that the trend of modern research is more and more in the direction of producing or isolating substances (*a*) which may have been of commercial or pharmaceutical value, (*b*) which may prove useful as synthetic intermediates or degradation products of more complex natural substances, or (*c*) which may help indirectly in elucidating the constitution of such complex compounds.

The active research centres where work on phytochemistry was done in the past and is also being carried out at the present are stated below with their major subjects of interest.

School of Tropical Medicine, Calcutta

Under the efficient supervision of Col. R. N. Chopra (1921-1939), a school on phytochemistry flourished in this Institution. Chopra with his eminent collaborators, viz., S. Ghosh, B. Mukherjee, N. K. Dey, and B. S. Kahali, made an extensive study on Indian plants with special reference to the isolation of plant products and their pharmacology. A survey of the work carried out in the School of Tropical Medicine has appeared in several books written by Chopra who is still pursuing researches on Phytochemistry in the Regional Research Laboratory, Jammu-Twai, and Kashmir. The books written by Chopra[3a] also include a fairly complete bibliography practically from the time when phytochemical work was started in India.

S. Ghosh[1] studied several alkaloid bearing plants and isolated cardiac glycosides from *Nerium oleander* Linn.

R. N. Chakravarti[4,5], who succeeded Ghosh, has isolated a known sapogenin, diosgenin, from several species of *Dioscorea*. Chakravarti and his collaborators studied arborine[4,5] (=glycosine), a quinazoline base from *Glycosmis arborea* and elucidated the structure of aegelin (confirmed by synthesis[4,5]), an alkaloid amide occurring in the leaves of *Aegle marmelos* Correâ from which they also obtained γ-sitosterol. Chakravarti and his group in collaboration with Robert Robinson studied the constitution of echitamine and proposed a strychnine structure for this base[3b] (cf. Ref. 16, 17).

University of Lahore

Research on Phytochemistry was initiated in this University by J. N. Ray (1928-1940). He did many valuable researches on the synthesis of isoquinoline alkaloids (Fam. *Berberidaceae*) and was the first to prove that vasicine[6], the quinazoline alkaloid of *Adhatoda vasica* Nees. occurs in the family, *Acanthaceae*. This study has significant contribution on the biogenesis of alkaloids. Ray also studied the chemistry of rottlerin, the chief phenolic crystalline component of "Kamala". His latest contribution in the structural elucidation of chaksine, an alkaloid of *Cassia absus* Linn. which is still a confronting problem is really commendable. Besides these, Ray developed a good procedure for the storage of opium, the poppy plant extract and to prevent loss of morphine content and has prepared citric acid ferment from the lower plant, *Aspergilus*.

The syntheses of corydaldine and santene glycol by Ray have been considered to be "elegant". The synthetic experiments on oreoselone and other furo-coumarins have attracted considerable attention.[6a]

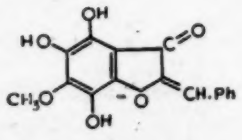
University of Allahabad

S. B. Dutt (1925-1944) worked mainly[3] on isolation problems and studied in a few cases the constitution of the plant-products[1,4]. He investigated various plants, viz., *Aegle marmelos* Correâ, *Glycosmis pentaphylla* Correâ, Indian Kamala (*Citrus aurantium*), *Citrullus colocynthis* Schrad., *Nyctanthes arbortristis* Linn., *Lageneria vulgaris* Seringe, *Terminalia arjuna* W. & A., etc., from which many crystalline compounds (rottlerin, ∝-clatorin, mannitol, arjunin, etc.) were prepared and the properties of some of these constituents were reported. In 1945, he joined the University of Delhi where he continued researches in his own field till 1949.

Tibbi College, Delhi

S. S. Siddiqui (1928-1940) has extensive contribution in the field of Plant Chemistry[1,3,4]. The main theme of his investigation was (*a*) isolation of active principles from medicinal plants, (*b*) studies on their pharmacological action, and (*c*) elucidation of the active principles wherever possible. He specialised on alkaloid chemistry although many sterols, chalkones, flavonoids and bitter principles from plants were isolated in his laboratory. The most important work for which he gained world-wide reputation was on *Rauwolfia serpentina* Benth and *Holarrhena antidysenterica* Wall. These plants were shown to be rich storehouse of therapeutically active alkaloids which have secured a good place in modern medicine. Work on the plants: Chana, Nimblossom, *Psoralea corylifolia* Linn., *Euphorbia tirucalli* Linn., and *Cassia absus* Linn, also deserves mention.

Siddiqui studied the constitution af pedicinin[6b] isolated from *Didymocarpus pedicellata* R. Br, and assigned to it the structure (I).



(I)

University of Delhi

T. R. Seshadri who first initiated phytochemicol work in Andhra University is still pursuing researches in the same line in Delhi University with a large

number of collaborators[4,5]. His valuable and original contributions in the field of plant chemistry are outlined in the text, the main theme of which might be conveniently subdivided into the following groups:

(*a*) Plant colouring matters belonging to flavonoids, anthocyanins, anthoxanthins, and chalkones, etc.

(*b*) Lichens and mould products.

(*c*) Natural coumarins (4-phenylcoumarins from *Leguminosae* family).

(*d*) Biogenesis of flavonoids, coumarins and their derivatives.

(A) *Anthoxanthin glycosides and aglycones.*—This work was taken up by Seshadri with an idea to examine the correlation (if any) between the chemical composition and the botanical differentiation of the species and it appeared that there was. The investigation was started with members of the family, *Malvaceae*. He examined the pigments of the flowers of different species of *Gossypium* as also of *Thespasia populnea*, *Hibiscus cannabinus* Linn., and *H. sabdariffa* Linn. and later *H. vitifolius* Linn., and *H. esculentus* Linn.

(B) *Anthocyanins and anhydro-colour bases.*—A survey of plant sources included flowers of many garden plants, and forest trees, fruits such as the apple, lichi, jambul, pomegranate and chilies and agricultural plants such as the sugarcane and linseed. From these materials interesting informations were collected regarding the occurrence and properties of anthocyanins and anhydro-colour bases.

A recent study made by Seshadri relates to the components of the glumes of *Andropogan sorghum-durra* Linn. Two quinonoid anhydro-colour bases (Durrahodin and Durrarubin) have been isolated from these glumes. The former has been found to be the colour base of 7-hydroxy-8-methyl-4-methoxyflavylium chloride, the nature of the latter being a more complex one. Its properties and decomposition products indicate a flavylium structure with a trihydroxyphenyl ring attached to the 4-position. A comparison of the latter with a synthetic sample of 2,4-diphenyl-7-hydroxypyrilium chloride indicated their close similarity.

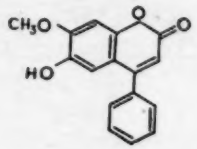
(C) *Leucoanthocyanidins.*—In recent years, Seshadri studied the chemistry of leucoanthocyanidins. (−) Leucopelargonidin has been isolated from *Eucalyptus calophylla* Kino. *Butea* gum has been shown to produce a (+) leucocyanidin, whereas tamarind seed testa (a large byproduct industry) contains another dextro-rotatory isomer. Their constitution still remains undetermined.

(D) *3-Hydroxyflavanones and catechins.*—The assignment of the dihydroflavanone structure has been ascribed to alpinone, fustin and ampelopsin. A number of such compounds has been found to occur in the heartwood and bark of trees, viz., pinobanksin, and taxifolin, etc. A detailed study of the association of flavonoids in plants showed that 3-hydroxyflavanones functioned as important intermediates in the biosynthesis of other flavonoids. It was shown by Seshadri that *l*-epicatechin occurs in a large number of Indian plants and has been considered to have vitamin-P properties.

(*E*) *Components of woods and related plant materials.*—Roots of *Decalepis hamiltonii* W. & A. and *Hemidesmus indicus* R. Br. were studied. They contain considerable quantities of triterpenes. *Derris* roots belonging to various species were examined in the light of plant insecticides and some work was done on the constitution of scandenin and robustic acid. *Pterocarpus marsupium* Roxb. was shown to contain a high percentage of pterostilbene which seems to have antidiabetic properties.

The study of the heartwood of *Dalbergia sissoo* Roxb. is of particular importance since it has yielded simple members of a new group of coumarins, viz., 4-phenylcoumarins.

Dalbergin (II) and methyldalbergin belonging to this group possess substituents in the 6- and 7-positions.



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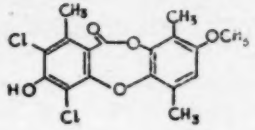


(III)

(F) *Naturally occurring flavones and flavonol methyl ethers.*—Flavonoid methyl ethers, particularly their partial methyl ethers, widely occur in nature and have been found to have important physiological action, e.g., calycopterin has been shown to be an anthelmintic. Patuletin occurring as its glycoside was studied and was established as the 6-methyl ether of quercategetin. Extraction of 'tambul' seed yielded tambuletin, first isolated by Bose (vide ref. 27) from this source. It was shown to be a monomethyl ether of herbacetin.

Besides these, Seshadri has considerable contribution in the chemistry of lichens (*Parmelia* species) and mould products. From the lichen *Toloschistes flavicans*, a colorless compound, vicanicin, has been isolated and shown to possess the structure (III).

Quinones, xanthones, and chromones etc., have received his attention and the suggestion regarding the possible biosynthetic pathways of flavonoids, coumarins, furanocoumarins and chromeno-α-pyrones may also be recalled[6c].

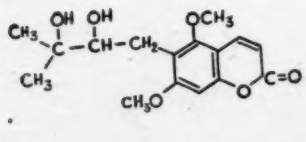
Madras Presidency College

During 1928-1944 B. B. Dey studied coumarins and alkaloidal principles of several plants, mention-worthy of which are *Toddalea acculeata* Pers. and *Hedyotis auricularis* Linn. The most interesting coumarin that he investigated was toddalolactone[3] (IV) having hydrated isopentenyl chain in phenyl nucleus.

A brief account of the work of T. R. Govindachari on plant products carried out in the Madras Presidency College is stated below.

Of various plant products: (*a*) alkaloids of pyridine, isoquinoline, and phenanthridine series, (*b*) coumarins, and (*c*) terpenes, continue to dominate his interest[4,5].

Govindachari, (the successor of Dey elucidated the constitution of ethylcarpyrinate (a degradation product of carpaine) on the basis of selective oxidation studies followed by synthesis. Gentianine, an alkaloid of *Enicostemma littorale* Blume (*Gentianaceae*), was shown to be 4-2′-hydroxyethyl-5-vinylnicotinic lactone Recently he established the constitution of the complex alkaloid, tylophorine[7] (V).



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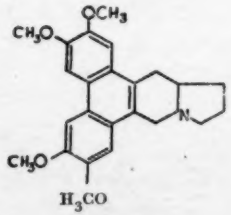
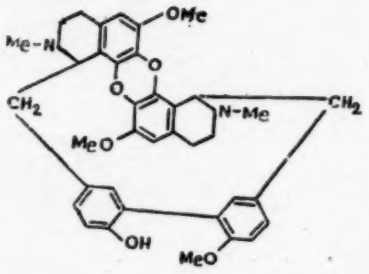


(V)

the major alkaloid of *Tylophora asthmatica* W. & A. (*Asclepiadaceae*). The base has been shown to be 2,3,6,7-tetramethoxyphenanthro (9,10,6′,7′) indolizidin The minor alkaloid, tylophorinine[8], occurring in the same plant has been converted to dimethyl-2, 3, 6-trimethoxyphenanthrene-9, 10-dicarboxylate. The constitution of a new alkaloid, reticuline, isolated from *Annona reticulata* Linn. has been established as 2-methyl-7-hydroxy-6-methoxy-1-(3-hydroxy-4-methoxybenzyl)- 1,2,3,4-tetrahydroisoquinoline.

Tiliacorine, the major alkaloid of *Tiliacora racemosa* Colebr. was assigned the structure (VI).



(VI)

Besides alkaloids, Govindachari and his associates have studied the chemistry of a few bitter lactones.

A new member of this group, wedelolactone, was isolated from *Wedelia calendulacea* Less. (*Compositae*). From various degradative studies, it was shown that wedelolactone is the lactone of 5,6-dihydroxy-2 (2,6-dihydroxy-4-methoxyphenyl)-benzfuran-3-carboxylic acid. The synthesis of its parent ring and of its tri-*O*-methyl derivative were also achieved.

Another lactone, feronia lactone isolated from the root bark of *Feronia elephantum* Correâ, was identified as the geranyl ether of umbelliferone.

Mention should also be made about his recent work on echitamine[9,10] and on jatamansone (a bicyclic terpene ketone from *Nardostachys jatamansi* DC. well reputed to produce sedative action).

University of Kerala, Trivandrum

The major interest of P. P. Pillay[4,5] is centered around the domain of (*a*) essential oils, (*b*) terpenes, and (*c*) alkaloids with special reference to their isolation and characterisation. The constituents of the essential oils of *Cymbopogon coloratus* Staff., *Cedrela toona* Roxb., *Anacardium occidentale* Linn., etc., were investigated and their possible uses were suggested. Among the terpene bearing plants, studied by him, mention may be made of *Pinus longifolia* Roxb. and Japanese *Mentha*. A number of alkaloid bearing plants, viz., *Holarrhena antidysenterica* Wall., *Strychnos nuxvomica* Linn., *Chonemorpha macrophylla* Wall, *Vinca rosea* Linn., and *Rauwolfia micrantha* Hook.f. were also examined by Pillay with a view to examining the nature of their basic components. Besides, he studied a number of complex phenols (from *Semecarpus anacardium* Linn.) and acids (from *Emblica officinalis* Gaertn.) for their commercial and therapeutic values.

Bose Institute, Calcutta

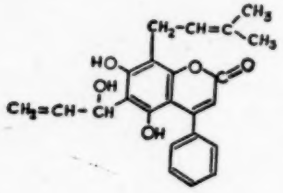
P. K. Bose, during his stay in the University of Calcutta (1934-1942) carried out valuable research work on phytochemistry. He is still actively pursuing research in his own subject [4,5,11] at Bose Institute. His major interest is on (*a*) coumarins, their biochemical properties, (*b*) flavonoids, and (*c*) bitter furanoids. Bose examined the following plants:

Piper chaba Hunter, *Ananas sativus* Schult, *Eupatorium ayapana* Vent, *Aegle marmelos* Correâ, *Luvunga scandens* Buch-Ham., *Murraya exotica* Linn., *Glycosmis pentaphylla* Correâ, *Oroxylum indicum* Vent, *Phebalium argenteum* Sm., *Xanthoxylum acanthopodium* DC. *Blumea eriantha* DC., *Ferula alliacea* Boiss, *Didymocarpus pedicellata* R.Br., *Paederia foetida* Linn., *Aegiceras majus* Gaertn., *Heracleum concanense* Dalz., *Ficus* species, *Luffa cylindrica* M. Roem., etc.

He isolated 2,2-dimethyl-$\triangle^3$-chromeno-α-pyrone of angular configuration from *Seseli indicum* W. & A., 8-methoxy-2,2-dimethyl-$\triangle^3$-chromeno-α-pyrone from *L. scandens* Buch-Ham., and psoralene from *Phebalium argentum*.

The constitution of gardenin[12], the flavone from *Gardenia lucida* Roxb., was postulated as 5-hydroxy-3,6,8,3′,4′,5′-hexamethoxyflavone or its isomer 5-hydroxy-3,7,8,3′,4′,5′-hexamethoxyflavone (cf. ref. 6c).

From *Mesua ferrea* Linn. P. K. Bose and D. P. Chakraborty have isolated a new 4-phenylcoumarin, mesuol (VII).



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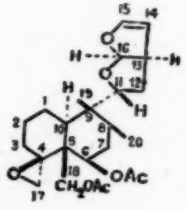


(VIII)

Bose and Banerjee studied the chemistry of clerodin, the bitter principle of *Clerodendron infortunatum* Linn. (Fam.: *Verbenaceae*). Robertson *et al.*[12a] as well as Barton and his collaborators[12b] have shown that clerodin has the structure (VIII).

It was also shown by him that 7-methoxycoumarin possesses a strong haemostatic property and many natural coumarins exhibit remarkable antibiotic activities.

Bose during his stay in Lac Research Institute (1944-1954), studied the constitution of shellac and showed that butolic acid is one of its constituents.

Besides these, work on triterpenes[4,5] is also being carried out in this Institute.

University of Dacca

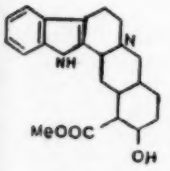
During 1925-44 in Dacca, there were several active groups of workers[3] of which mention many be made about S. S. Guha Sircar, N. K. Sen, J. K. Chaudhury and P. B. Sarkar. S. S. Guha Sircar studied the bitter principles of *Caesalpinia bonducella* Fleming, *Andrographis paniculata* Neés. and *Swietenia macrophylla* King. N. K. Sen examined the fixed oils and bitter principles of the seeds of *Corchorus olitorius* Linn. which possesses cardiac action. J. K. Chaudhury and P. B. Sarkar investigated the lignin content in jute and the chemistry of its cellulosic fibres where the cementing matters have been found to consist of polymerised hexoses and pentoses combined with uronic acids.

University of Calcutta

Work on natural products[1,2,3] with special reference to natural colouring matters, essential and fixed oils, flavones and coumarins was initiated in this University by P. C. Mitter, M. N. Goswami (1928-1957), and P. K. Bose (*vide infra*).

Mrs. Asima Chatterjee has been pursuing researches in the field of Indian medicinal plants in this University for more than two decades[4,5,13,14]. Her main interest is on (1) alkaloids belonging to the following series: isoquinoline, β-carboline, quinazoline, pyrrolidino-indoline, steroid and diterpenoid together with their structure-activity relationship, (2) coumarins, and (3) bitter furanoids. Chatterjee and her collaborators are the first to observe that, (*a*) β-carboline alkaloids of yohimbine series occur in the family *Apocynaceae;* (*b*) pyrrolidino-indoline in *Apocynaceae;* (*c*) Wieland-Gumlich aldehyde, i.e., Strychnine type base in *Apocynaceae;* (*d*) Simple quinazoline in *Rutaceae;* (*d*, Diterpene alkaloid in *Compositae;* (*f*) Indole-quinazoline base in *Xanthoxylum* species; (*g*) Steroidal alkaloid in *Chonemorpha* plants.

Several medicinal plants[5] (nearly seventy) belonging to different botanical families (mostly *Apocynaceae*, *Rutaceae*, *Compositae*, and *Umbelliferae*) have been examined chemically. Some of these have eventually been found to be promising vegetable drugs, e.g., *Rauwolfia canescens* Linn., *R. serpentina* Benth., *R. micrantha* Hook.f., *R. beddomei* Hook. f., *R. densiflora* Benth & Hook., *Kopsia albiflora* Linn., *Alstonia scholaris* R. Br., *Chonemorpha macrophylla* Wall, *Vinca rosea* Linn., and *Aegle marmelos* Correâ, etc. Most of these plants have received clinical application for their therapeutic efficacy. The alkaloids which were isolated for the first time and the constitution of which was established, are: rauwolscine[15] (IX), rauwolfinine[15a] (X), serpinine (XI) and sarpagine (XII), belonging to β-carboline alkaloids having sedative and hypotensive properties. Besides these, she has examined various other *Rauwolfia* species of India and abroad from which a number of alkaloids, viz., δ-yohimbine and its congeners were isolated and studied.



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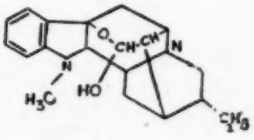

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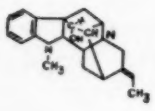

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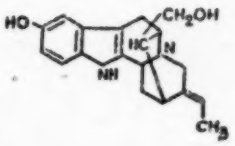
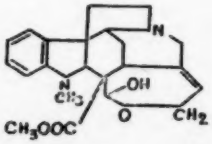


(XII)

Kopsine (XIII), the strychnine-type alkaloid isolated from *Kopsia albiflora* Linn., has been shown to have curariform activity. Echitamine[16,17] (XIV), which possesses an unusual skeleton and occurs in *Alstonia* species, has been shown to be an alkaloid of eserine



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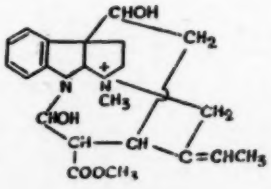
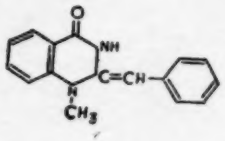


(XIV)

type which has been later confirmed from X-ray crystallography by J. M. Robertson[17a] of Glasgow University. The occurrence of this heterocyclic moiety is observed for the first time in the family *Apocynaceae*.

The constitution of several quinazoline alkaloids, viz., glycosine (XV) (*from Glycosmis pentaphylla* Correâ) and aegelenine[18] (XVI) (*from Aegle marmelos* Correâ), has been fully



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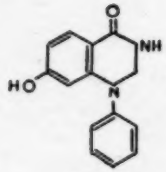
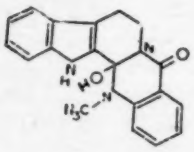


(XVI)

established. It has been shown by Chatterjee and her research associates that rhetsinine (XVII), rhetsine (=evodiamine) and rhetine(=rutaecarpine) occurring in *Xanthoxylum rhetsa* DC. are indole-quinazolines by their degradative studies as well as by synthesis.



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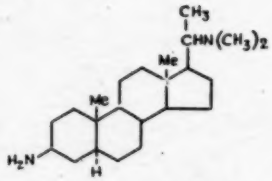
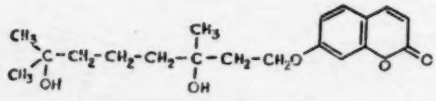


(XVIII)

The steroidal alkaloid, chonemorphine, a promising hormonal drug, has been isolated from *Chonemorpha macrophylla* Wall. The constitution of chonemorphine[19] (XVIII) has been established from the degradative studies and also from its total synthesis.

A new observation has been made with *Inula royleana* DC. belonging to the family *Compositae*. It has been shown that the diterpene alkaloids, royline (=lycoctonine) and inuline (=anthranoyllycoctonine) occur in this family[20].

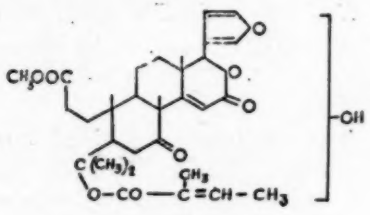
The investigation on the constitution of a new coumarin, marmin[21] (XIX), as also studies on the stereochemistry and new synthesis of aegeline[21a], an alkaloid amide (both isolated from *Aegle marmelos* Correâ) deserves mention. Bergamottin[22] and a few naturally



(XIX)

occurring coumarins have recently been synthesised. Her researches in the field of lactones culminated in the elucidation of the structure of swietenine (XX) (from *Swietenia macrophylla* King; Fam. *Meliaceae*) and tinosporine, the bitter principle of *Tinospora cordifolia*

Miers (Fam. *Menispermaceae*). From I.R. and X-ray diffraction studies tinosporine has been shown to be identical with columbin.



(XX)

Attention has also been drawn in the laboratory of Chatterjee towards the syntheses of naturally occurring alkaloids under "Physiological conditions". The synthesis of calycotomine[23] (1-hydroxymethyl-6,7-dimethoxy-tetrahydroisoquinoline) needs mention in this connection.

From *Prunus puddum* Roxb. ex Wall, D. Chakravarti and N. Kundu[23a], another group of workers, isolated puddumetin (flavone), prunasetin (isoflavone), and sakuranetin (flavanone) in 1948.

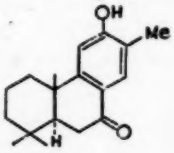
M. M. Chakrabarty and his associates of the same University are carrying on researches[4,5] on the component fatty acids and glyceride composition of oil seeds of Indian plants, viz., *Cajanus cajans* (linoleic acid), *Citrullus colocynthis* (linoleic acid), and *Corchorus olitorius*,etc.

Presidency College, Calcutta

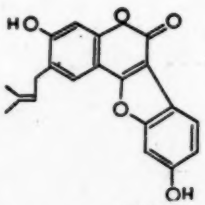
During the fifties R. Chatterjee carried out interesting work on Phytochemistry in Presidency College, Calcutta. His primary contribution was directed towards the field of isoquinoline alkaloids[4,5]. He investigated several plants of *Mahonia* genus amongst which the following deserve mention. *M. acanthifolia*, *M. simousii* and *M. berealis*. These species were found to contain the alkaloids, oxyacanthine, berberine, neprotine, palmatine and jatrorrhizine. Umbellatine (=berberine) and neprotine (=jatrorrhizine) were obtained from *M. nepalensis* DC.

East India Pharmaceutical Works, Calcutta

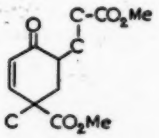
P. Sen Gupta and H. N. Khastgir along with their collaborators have taken up an extensive research programme on Indian medicinal plants. Special mention should be made about the elucidation of the complete structures of two natural products, viz., nimbiol[24] (XXI) and psoralidin[25] (XXII). The constitution of nimbiol has received confirmation from the synthesis of its (±) *O*-methyl derivative by French[26] and American[26a] workers as early as 1930 and later by Indian Workers[26b] in the same year. The structural elucidation of



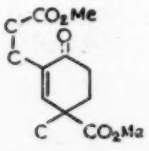
(XXI)



(XXII)



(XXIII)



(XXIV)

nimbin[24] by these workers is, indeed, commendable. Nimbin has been shown to possess either of the two partial structures (XXIII) or (XXIV).

National Chemical Laboratory, Poona

Under the supervision of its Director, K. Venkataraman,[4,5,27], phytochemical work in N. C. L. is making rapid strides. Researches on three different sections of natural products are being pursued in this Institution:

I. Natural Dyestuffs belonging to anthocyanins, flavonoids, and anthraquinones.

II. Essential Oils of terpene series.

III. Coumarins, flavones, isoflavones, and xanthones, etc.

Research on Dyestuffs is being conducted by Venkataraman. From the wood of *Artocarpus integrifolia* Linn. several flavones, viz., artocarpin and isodehydroartocarpin, artocarpetin and artocarpanone have been isolated and their constitutions have been elegantly established. Artocarpetin has been proved to be 5,2′,4′,-trihydroxy-7-methoxyflavone. Artocarpin has the same nuclear skeleton where 3-position is substituted by the group $—CH_2\text{-}CH=CMe_2$ and 6-position by $Me_2CH\text{-}CH=CH—$. In isodehydroartocarpin, 3-alkenyl group and 2′-hydroxyl have undergone a cyclisation.

Two new flavonols, pinoquercetin and pinomyricetin, were isolated from *Ponderosa* pine bark and their constitution was shown to be 6-methylquercetin and 6-methylmyricetin. They are of special interest because only one *C*-methylflavone (strobochrysin, 6-methylchrysin) has so far been isolated from plants.

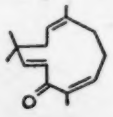
Isoflavones synthesised in Bombay laboratories by Venkataraman and his group were daidzein, formononetin, tectorigenin and muningin.

The physiological properties of naturally occurring anthraquinone and anthrone derivatives were also investigated. Morellin, the main colouring matter of the seeds of *Garcinia morella* Desr. has powerful antibacterial activity *in vitro*. Recent work has shown that morellin contains a 6-*iso*amylene-2,2-dimethyl-5,-7-dihydroxychromanone nucleus connected to a partially hydrogenated and alkenyl substituted naphthalene ring by an ∝-pyranone ring.

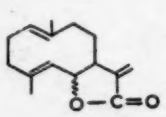
Essential Oils.—S. C. Bhattacharya in collaboration with K. K. Chakravarti and a group of active workers have been carrying on investigation on essential oils[4,5] of santalol series, *Aquilaria agallocha* Roxb., *Saussurea lappa* C. B. Clarke, Indian dill oil (*Foeniculum vulgare* Mill.), Vetiver oil, Malabar lemon grass, and *Mentha viridis* Linn., etc. The structures[4,5] of various terpenaceous compounds constituting these essential oils have been elucidated.

Zerumbone (XXV) isolated from the oil of Zingiber has been shown to be a monocylic sesquiterpene ketone and the structure and absolute configuration of costunolide[28] (XXVI) from *S. lappa* has also been established.

Sukh Dev[4] has studied the chemistry of terpenoids isolated from various essential oils and has recently made an important study on the proton magnetic resonance spectra of humulene, zerumbone and their derivatives. From n.m.r. data he has fixed up the precise location of the ethylenic linkage in humulene.



(XXV)



(XXVI)

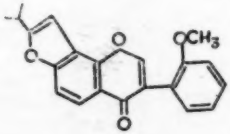
Coumarins, Flavones, Isoflavones and Xanthones.—From Indian flora several flavones and xanthones were isolated by R. C. Shah[4,5] (from 1934 onwards) and his associates. They obtained from *Oroxylum indicum* Vent. a 5,7-dihydroxy-6-methoxyflavone. Oroxylin-A, a companion flavone, was proved to be a 6-*O*-methyl-baicalein (5,7-dihydroxy-6-methoxyflavone). The constitution of calycopterin, the yellow colouring matter of the leaves of *Calycopteris floribunda* Lam. was considered to be a 4,5-dihydroxy-3,6,7,8-tetramethoxyflavone.

Swerchirin, a new xanthone from *Swertia chirata* Buch.-Ham. was proved to be the dimethyl ether of 1,3,5,8-tetrahydroxyxanthone. *Swertia decussata* Nimmo ex Grah., a plant which is used as a substitute for 'chirata' yielded decussatin and swertenin. From degradative and synthetic studies it was confirmed that swertinin and decussatin are the di- and tri-methyl ethers respectively of 1,3,7,8-tetrahydroxyxanthone.

Geigerin, a naturally occurring coumarin, was proved to be 7-methoxy-6-isovaleryl coumarin by its synthesis.

J. L. Bose[4,5] of the same laboratory has established the identity of biochanin-A and biochanin-B (the isoflavones from "chana") with 5,7-dihydroxy-4'-methoxyisoflavone and 7-hydroxy-4'-methoxyisoflavone respectively. He has also studied the oestrogenic activity of biochanin-A and related products.

N. L. Dutta[29] of the same research institution has elegantly established the structure of munetone (XXVII), the active principle of *Mundulea suberosa* Benth. (Fam. *Leguminosae*).



(XXVII)

Central Drug Research Institute, Lucknow

Intensive work on plant products is being done in Central Drug Research Institute, Lucknow, where M. L. Dhar and his associates[4,5] have been carrying on researches on (1) alkaloids, (2) glycosides, and (3) saponin bearing plants as also on other miscellaneous natural products with the object of examining their therapeutic properties.

The structure of alangine-A[30] (from *Alangium lamarckii* Thw.) has been proposed to be 3-anisyl-2-piperidyl-*n*-propanol. Two alkaloids, hayatin and hayatinin were isolated from *Cissampelos pariera* Linn. Of these the former has been shown to be a bis-benzylisoquinoline base. *Cyclea burmanni* Hook. yielded an alkaloid identical with tetrandine.

From *Rauwolfia canescens* Linn., they isolated sarpagine and raunescine. The bases of *Stephania glabra* Miers were shown to be palmatine and tetrahydropalmatine.

The glycosides and saponins of the following plants have also received their attention:

Achyranthes aspera Linn., *Caesalpinia digyna* Rottl., *Centella asiatica* Linn., *Ailanthus malabarica* DC., *Erythrina indica* Lam., *Melodinus monogynus* Roxb. *Picrorhiza kurrooa* Benth. gave two glycosides, kutkin, 6-cinnamoyl-α-D-glucosidovanillate, and kurrin, containing D-mannitol in the glycosidic portion. Besides these, various other crystalline components of varying degrees of therapeutic values have been isolated from other plant materials.

Regional Research Laboratory, Jammu-Tawi, Kashmir

R. N. Chopra[1,4,5] and his collaborators, I. C. Chopra, K. L. Handa, L. D. Kapoor and others are studying extensively the flora of N.W. Himalayan region with special reference to the isolation and pharmacology of plant products. This work is mainly on the phytochemistry of (I) Poisonous Plants (Poisonous to Live-stocks and Human beings); (II) Essential oil bearing plants (Aromatic Plants); (III) *Dioscorea* species for the production of diosgenin; (IV) Toxicology of Indian cryptogams (or flowerless plants) and phanerogams; (V) Insecticidal and insect-repelling plants, besides various vegetable drugs as also their microbiological investigation.

Forest Research Institute, Dehra Dun

The chemistry of (1) Essential Oils, (2) Plant-pigments, and (3) Plants of established commercial (wood and other cellulosic substances) and therapeutic values are studied here. P. S. Rao[4] and S. Krishna besides others are active workers in this field.

The work of S. V. Puntambekar and Sadgopal[4,5] on the composition of essential oils and fixed oils, needs mention in this connection.

Indian Institute of Science, Bangalore

Studies on various essential oils initiated by P. C. Guha[3-5] are still being pursued in this Institution by B. H. Iyer[4,5] and his associates. In this centre considerable work on fixed oils isolated from various plant sources was done by J. L. Simonsen (*vide supra*) and P. R. Iyer.

University of Andhra, Waltair

The interests of L. Ramachandra Row[4,5], an active research worker in plant chemistry, (since 1950) centre round flavonoids, triterpenoids, and alkaloids. To his credit may be mentioned the isolation, characterisation and synthesis of three new furanoflavones from *Pongamia pinnata* (L) Merr. and rutin from *Bauhinia tomentossa*. It was pointed out that the latter plant could form a commercial source for rutin. The peels of *Citrus mitis* Blanco. yielded hesperidin, 5-*O*-desmethyl nobiletin and two new flavanones, citromitin and 5-*O*-desmethylcitromitin. Citromitin was shown to be 5,6,7,8,3′,4′-hexamethoxyflavanone and may be of considerable significance in the biogenesis of some *Citrus* flavonoids.

His examination of the local plants of *Menispermaceae* has resulted in the discovery of a new type of bis-benzylisoquinoline alkaloids with a diphenyl system. Row and his collaborators were the first to isolate tiliacorine and tiliarine from the roots of *Tiliacora racemosa* Colebr. and to show that they belonged to the new type of bis-benzylisoquinoline alkaloids. Trilobine was also isolated from the roots of *Cocculus hirsutus* Diels.

In a scheme on the chemical examination of the local timbers to explain the fungal and white ant resistance, 3-hydroxy-2-methylanthraquinone was isolated fom the common teak, *Tectona grandis* Linn., and an entirely new triterpenoid from *Terminalia tomentosa*. By a systematic study, the latter was shown to be 19-hydroxy arjunolic acid. *T. arjuna*, *T. belerica* and *T. paniculata* were also examined. *Diospyros melanoxylon* and *Adina cordifolia* were also investigated under the above scheme.

S. Rangaswami[4,5] has been pursuing researches in this centre primarily on flavonoid glycosides, lichens, triterpenes and related plant products.

The following plants were investigated:

Tephrosia lanceolata, *T. candida* DC., *T. hirta* Ham., *Usnea hirta*, *U. florida*, *Urginea indica* Kunth., *Entada scandens* Benth., *Parmelia tinctorum*, *Digitalis lanata* Ehrh., *Cerbera odollam* Gaertn., and *Ramalina farinacea*, etc. From *Rhododendron falconeri* Hook,

two triterpenes (ursolic acid and *epi*friedelinol) and a glycoside of quercetin (hyperoside) were isolated and characterised. "Maxima-substance-A" isolated from *Tephrosia maxima* Pers. has been shown to be a dimethylenedioxy*iso*flavone. Two crystalline glycosides, viz., peruvoside and ruvoside, from *Thevetia nerifolia* Juss., considered to be digitaloid glycosides, have been isolated. The constitution of vogeletin, the pigment of *T. vogelii* Hook. was established as 6-methoxy-3,6,7,4′-tetrahydroxyflavone.

The phenanthridine alkaloid, lycorine, was also isolated by Rangaswami from *Crinum defixum* Ker-Gawl., and *Crinum latifolium* Linn.

Lac Research Institute, Ranchi

Major problem studied in connection with lac research[4] is on the following:—

(*i*) The constitution of lac with a view to improving its properties for industrial development.
(*ii*) Preparation of good qualities of lac and its behaviour towards bleaching agents,
(*iii*) Constitution of lac dye.
(*iv*) Increase of production of lac from *Butea frondosa* Koen (Palas) and *Schleichera oleosa* Merr. (Kosum) by varying ecological and other factors.

An elegant review[31] on Lac and Shellac has been published by the Indian Lac Cess Committee, Ranchi, wherefrom the detailed information on this subject would be available.

Plant Genesis

Phytochemical research done in the past and at present has divulged many secrets of nature: the properties of cellular constituents of plants, the characteristic features of many botanical families, and their biogenetic relationship. An outline of these studies* made so far is presented below and it will give an idea about plant genesis.

TABLE I

Alkaloid-bearing plants.

Family	Nature of the compounds studied.
Acanthaceae ..	Quinazoline
Amaryllidaceae ..	Phenanthridine
Anonaceae ..	Isoquinoline
Apocynaceae	(1) Indole group:
	(*a*) Yohimbine type (∝)
	(*b*) Strychnine type (β)
	(*c*) ∝ & β types with several variants
	(*d*) Pyrrolidinoindoline type (Eserine pattern)
	(*e*) Ibogaine type.
	(2) Steroidal alkaloid(alkamines)
Asclepiadaceae ..	Phenanthrine-indolizidine
Berberidaceae ..	Isoquinolines
Boraginaceae ..	Pyrrolizidine
Cactaceae ..	Isoquinolines and β-Phenylethylamines
Campanulaceae ..	Piperidine
Caricaceae ..	Isoquinolines
Chenopodiaceae ..	Napthaphenanthridine
Convolvulaceae ..	(1) Piperidine-pyrrolidine
	(2) Indole
Compositae	(1) Diterpene
..	(2) Pyrrolizidine
	(3) Pyrrolidino-pyridine
Cornaceae ..	Piperidine
Dioscoreaceae	Piperidino-pyrrolidine
Ephedraceae ..	β-Phenylethanolamines.
Euphorbiaceae ..	Piperdine
Fumariaceae ..	Isoquinoline
Gentianaceae ..	Pyridine
Gramineae	(1) β-Phenylethylamines
	(2) Indole
	(3) Pyridine
Lauraceae ..	Isoquinoline
Leguminosae ..	(1) Quinolizidine (Lupine type)

*"The Wealth of India' published under the auspices of the Council of Scientific and Industrial Research contains a comprehensive account of the results of work on plants.

TABLE I (contd.)

Alkaloid-bearing plants.

Family.	Nature of the compounds studied.	Family.	Nature of the compounds studied.
Leguminosae	(2) β-Phenylethylamine	Piperaceae ..	Piperidine
	(3) Pyrrolizidine	.. Ranunculaceae	(1) Diterpene alkaloids
	(4) Isoquinoline		(2) Isoquinoline
	(5) Bases with terpene moiety	Rubiaceae ..	(1) Quinoline (quinine etc.)
	(6) Indoles		(2) Isoquinoline
	(7) Pyridine		(3) Indole (and indole of ∝-type
Liliaceae ..	Alkamines, phenanthridine and colchicine type	.. Rutaceae ..	(1) Quinazoline
			(2) Alkaloidamide
Lineae ..	Piperidino-pyrrolidine		(3) Indolequinazoline
Loganiaceae ..	β-Type indole base (Indoline group: e.g., strychnine)		(4) Isoquinolines
			(5) Furoquinoline
			(6) Acridine
Lythraceae ..	Piperidine and dipiperidine	Solanaceae ..	(1) Pyrrolidono-piperidine (bicyclic).
Magnoliaceae ..	Isoquinoline		
Menispermaceae	(1) Bisbenzylisoquinolines		(2) Steroidal alkaloid (Alkamines)
	(2) Isoquinoline		
Palmeae	..(1) Pyridine		(3) Steroidal base with glycosidic unit
	(2) Colchicine types		
Papaveraceae	..(1) Isoquinoline		(4) Pyridine
	(2) ∝-Naphthaphenanthridine		(5) Pyrrolidino-pyridine

TABLE II

Triterpene, coumarin, bitter furanoid, glucosides, flavonoids, and steroid-bearing plants.

Acanthaceae	Dioscoreaceae	Leguminosae	Piperaceae
Apocynaceae	Ericaceae	Liliaceae	Rutaceae
Burseraceae	Euphorbiaceae	Malvaceae	Sapindaceae
Compositae	Ficoideae	Meliaceae	Simarubeae
Convolvulaceae	Guttiferae	Menispermaceae	Umbelliferae
Cucurbitaceae	Lecythidaceae	Oleaceae	Verbenaceae
			Zingiberaceae

TABLE III

Essential oil-bearing plants

Araceae	Cupressineae	Labiateae	Palmeae
Aristolochiaceae	Cyperaceae	Leguminosae	Rutaceae
Chenopodiaceae	Euphorbiaceae (also rich in fixed oils)	Lauraceae	Santalacea
Compositae	Gramineae	Lythraceae	Thymelaceae
Coniferae	Guttiferae	Myristiceae	Umbelliferae
Cupuliferae	Fumariaceae	Oleaceae	Verbenaceae
			Zingiberaceae

Work on Indian Essential oils has been reviewed by A. K. Menon where the researches in this field by D. R. Dhingra, N. N. Godbole and others have been discussed[32] including his own.

This short review on Indian Phytochemistry is by no means comprehensive and, as indicated above, it is only a few of a number of topics in the field of plant chemistry which is being investigated in various active centres in India.

The work done on the medicinal, aromatic, and poisonous plants, the difficulties encountered and partially overcome during the investigation, and indications in regard to their utilitarian and scientific aspects will stimulate interest in this subject which is of great national importance. India possesses a rich and extensive forest resources, with varied types of vegetation as the dry deciduous, moist deciduous, moist evergreen, subtropical, temperate and Alpine. A survey of Indian flora, which is yet to be complete, has shown that India produces 11,000 botanical species of which only a few hundreds (nearly 600 species) have been examined. India's vegetable materia medica offers, therefore, a vast field of study and all that has been done to-date can be considered to have touched only the fringes of this vast and complex problem. Attention is yet to be paid towards poisonous plants occurring in nearly 90 families (belonging to both Cryptogams and Phanerogams) and aromatic plants which occur in 28 families. Particular care should also be taken in future on alkaloid bearing herbs because alkaloids are, generally, physiologically active and might turn out to be potent drugs in the therapy of many a malady. However, it must be admitted that with the growth of chemical laboratories in Universities, National Institutes, various Research Centres (National Cancer Research Centre, Calcutta, etc.), and Pharmaceutical Institutions, considerable progress has been made in exploring the potentiality of medicinal plants used in indigenous medicine. This work has brought out the merits of various Indian herbs which have secured a formidable place in world medicine. Importance of phytochemistry has been recognised not only in India but throughout the world because of its intimate relationship with medicine. From time to time, evaluation of this branch of chemistry is being made by the International Union of Pure and Applied Chemistry by holding Symposia on the subject. The world scientists are taking great interest in medicinal plants of India, and research on indigenous drugs of late years has extended even to the western countries. A serious effort should, therefore, be made for proper development of Phytochemistry in our country which obviously needs collaboration amongst systematic botanists, chemists, and pharmacologists supplemented with requisite financial assistance.

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Rubeanic Acid and its Derivatives as Chelating Ligands and Analytical Reagents

Priyadaranjan Rây* and J. Xavier†

Rubeanic acid or dithio-oxamide, although its lead salt was first described by Wöhler[1] in the early 1825, remained, however, practically in the dark, relating to its reaction with metallic ions, till a century later Rây and Ray[2] in 1926 revealed its usefulness and potentiality as a reagent for the detection of traces of cobalt, nickel, and copper with which it was found to form intensely and characteristically coloured complexes[3]. Since then the reagent has received considerable attention from various workers, particularly within the last few years, for use as a chelating ligand in colorimetric analysis and spot reactions of metals. Not only the parent compound, but many of its substituted derivatives have also been investigated for the purpose with a view to improving the selectivity of the reagent and the solubility of the coloured complexes formed. The structure of the metal chelates has also been under close examination and evidences have been recorded about the possibility of their forming long-chain polymeric molecules. But the analytical application of the reagent and many of its derivatives for spectrophotometric determination of a number of transition metals has received by far the wider attention and interest.

In recent years rubeanic acid and its derivatives, as well as their metal complexes, are being investigated for application in many other fields, and suggestions have already been made for their uses as metal deactivators, pigments, accelerators in vulcanization, ingredients for duplicating processes, herbicides, rodent repellents, organic intermediates, etc.

With a view to stimulating further interest in this interesting series of compounds with possibilities for application in diverse fields of pure and applied chemistry, it appears to be the right time for an attempt to collect and assess all pertinent information relating to the study of rubeanic acid and its derivatives and of their metal complexes in the form of a short review.

Furthermore, we feel that the right place for its publication will be in the Acharya Prafulla Chandra Rây Birth-Centenary Celebration Number of the Journal of the Indian Chemical Society, as the late Acharya Rây was greatly interested in the study of co-ordination complexes of many allied organic thio-compounds, particularly of the mercaptans and thioethers, with platinum metals.

Preparation

Rubeanic acid is prepared by passing dry cyanogen gas into an alcoholic solution of KSH (alcoholic KOH saturated with H_2S) in the cold. The solution is thereafter acidified

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with hydrochloric acid, when rubeanic acid is precipitated in the form of a red-brown product. This is then purified by recrystallization from 95% alcohol, using animal charcoal.[4-7]

In another method described in the literature[8,9], a concentrated solution of copper sulphate in aqueous ammonia is treated with potassium cyanide in the cold. The solution is filtered from any insoluble residue and saturated with H_2S. On cooling, the crystals of rubeanic acid separate. The yield is rather poor and the method is seldom used.

The reaction leading to the formation of rubeanic acid consists in the mere addition of hydrogen sulphide to cyanogen molecule. It may therefore be viewed as sulph-hydrolysis of cyanogen to form dithio-oxamide corresponding to the formation of oxamide from cyanogen by hydrolysis:

$$NCCN + 2H_2S \longrightarrow H_2NSCCSNH_2.$$

Alkyl-substituted rubeanic acids are obtained by warming rubeanic acid with the corresponding amine in aqueous or alcoholic solution[10-14].

$$H_2NSCCSNH_2 + 2RNH_2 \longrightarrow RHNSCCSNHR + 2NH_3.$$

It this manner *NN'*-dialkyldithio-oxamides containing straight-chain alkyl derivates from dimethyl to dioctadecyl as well as diallyl dithio-oxamides have been prepared. Branchde chain derivatives like diisopropyl, diisobutyl and dicyclohexylrubeanic acids have likewise been obtained[14]. Condensation of rubeanic acid with amines bearing other substituents, namely, ethanolamine, benzylamine, 3-dimethylaminopropylamine, 2-acetoxyethylamine and the sodium salts of aminoacetic acid and 2-aminoethylsulphonic acid (taurine), has led to the preparation of *NN'*-dibenzyl, *NN'*-bis-2-acetoxyethyl, 2-hydroxyethyl, 3-dimethylaminopropyl, carboxyethyl, and sulphoxyethyl dithio-oxamides[14]. *NN'*-Diphenylrubeanic acid was obtained along with the monothio-oxamide, $C_6H_5NHSCCONHC_6H_5$, by the action of phosphorus pentasulphide on oxanilide in boiling xylene. The dithio compound is separated from the monothio derivative by dissolving the product in dilute (5%) sodium hydroxide solution, followed by reprecipitation with carbon dioxide. The process is repeated several times. The final products are recrystallized from glacial acetic acid[15].

Properties

(1) *Physical.*—Table I records the appearance, melting point, and solubility of rubeanic acid and some of its derivatives. Solubility values are all quoted from Mallinckrodt Chemical Works Publication[14].

TABLE I

Reagent.	Appearance.	M.P.	Solubility (25°) (g./100 c.c.).
Rubeanic acid (Rba) $CSNH_2$ $CSNH_2$	Orange-red crystals	Decomp. at 140° without melting	Water (0.04), ethanol (0.56), methanol (1.0), acetone (3.2), chloroform (3.0), benzene (1.3), carbon disulphide (0.2), carbon tetrachloride (0.10), ethyl acetate (1.4)

TABLE I (contd.)

Reagent.	Appearance.	M.P.	Solubility (25°) (g./100 c.c.).
NN'-Dimethyl Rba $\begin{matrix}CSNHCH_3\\ |\\ CSNHCH_3\end{matrix}$	Yellow crystals	140° (138°)	Water (0.13), ethanol (1.5), methanol (2.0), acetone (11.5), chloroform (14.9), benzene (6.6), carbon disulphide (3.5), carbon tetrachloride (3.8), ethyl acetate (6.6).
NN'-Diethyl Rba $\begin{matrix}CSNHC_2H_5\\ |\\ CSNHC_2H_5\end{matrix}$	Yellowish red cryst.	58°	Resembles the dimethyl derivative in solubility; data wanting.
NN'-Diisoamyl Rba $\begin{matrix}CSNHC_5H_{11}\\ |\\ CSNHC_5H_{11}\end{matrix}$	Orange prismatic cryst.	59-60°	Do
NN'-bis-(2-hydroxy-ethyl) Rba. $\begin{matrix}CSNHCH_2CH_2OH\\ |\\ CSNHCH_2CH_2OH\end{matrix}$	Orange-yellow cryst.	93-94°	Water (1.0), ethanol (10.4), methanol (18.4), acetone (19.0), chloroform (0.32), benzene (0.18), carbon disulphide (0.10), carbon tetrachloride (0.10), ethyl acetate (3.5).
NN'-Dibenzyl Rba $\begin{matrix}CSNHCH_2C_6H_5\\ |\\ CSNHCH_2C_6H_5\end{matrix}$	Yellowish red cryst.	115° (110°)	Water (0.14), ethanol (0.25), methanol (0.25), acetone (4.9), chloroform (15.9), benzene (5.2), carbon disulphide (6.5, carbon tetrachloride (2.4), ethyl acetate (4.0).
NN'-bis-(carboxy-methyl) Rba. $\begin{matrix}CSNHCH_2COOH\\ |\\ CSNHCH_2COOH\end{matrix}$	Light brown powder	208.6°-210° (decomp.)	Water (0.77), ethanol (2.5), methanol (6.4), acetone (2.8), chloroform (0.18), benzene (0.20), carbon disulphide (0.22), carbon tetrachloride (0.18), ethyl acetate (0.85).
NN'-Dicyclohexyl Rba $\begin{matrix}CSNHC_6H_{11}\\ |\\ CSNHC_6H_{11}\end{matrix}$	Bright orange-red powder	146.3-148°	Water (0.12), ethanol (0.40), methanol (0.34), acetone (1.2), chloroform (24.4), benzene (8.5), carbon disulphide (18.8), carbon tetrachloride (13.8), ethyl acetate (1.70).
NN'-Didodecyl Rba $\begin{matrix}CSNHC_{12}H_{25}\\ |\\ CSNHC_{12}H_{25}\end{matrix}$	Straw-coloured powder	49.8°-51.8°	Water (0.06), ethanol (2.0), methanol (2.0), acetone (8.0), chloroform (53.0), benzene (43.5), carbon disulphide (57.0), carbon tetrachloride (46.0), ethyl acetate (13.0).
NN'-Diphenyl Rba $\begin{matrix}CSNHC_6H_5\\ |\\ CSNHC_6H_5\end{matrix}$	Shining orange-red plates	133° 134°	Resembles the dibenzyl derivative in solubility; data wanting.

The acidity constant, solubility product, and solubility of rubeanic acid were determined by potentiometric method[6] with the results: K_a (acid dissociation constant) =

$(1.28\pm0.04)\times10^{-11}$; Ksp (solubility product)$=3.9\pm0.12)\times10^{-14}$; and S(solubility)$=(3.07\pm0.04)\times10^{-3}$ mole per litre.

A consideration of the solubility data for rubeanic acid and its derivatives as given in Table I seems to suggest that although a polar substituent in the molecule more or less increases the solubility of the derivative in polar solvents and reduces its solubility in non-polar solvents, a non-polar substituent in the molecule, on the other hand, acts in the reverse way. This is rather a very rough approximation as several other factors are known to influence the phenomenon of solubility. Water being highly associated behaves somewhat anomalously in this respect.

Bradley and Cleasby[17] have studied the vapour pressure of rubeanic acid over a limited range of temperature (86.9-104.15°) and have determined its lattice energy and entropy of vaporization. The values obtained for the two latter are comparable to those of oxamide; the lattice energy value is, however, lower but the entropy value is slightly higher.

	Lattice Energy (cal/mole)	Entropy of vaporization (cal/degree/mole)
Oxamide	27,000	44.4
Rubeanic acid	25,200	45.0

The crystal structure of rubeanic acid has been studied by means of X-ray diffraction by Long *et al*[18].

The infrared spectra of rubeanic acid as also of its derivatives have been studied[14,19]. Rubeanic acid shows three strong bands at 3304, 3205, and 3135 cm^{-1}, and the spectrum resembles that of *N*-methylacetamide. The infrared spectra of rubeanic acid and its derivatives indicate that in the crystalline state they exist predominantly in the keto form.

(*b*) *Chemical Properties.*—Rubeanic acid and its derivatives are very weak acids, soluble in dilute aqueous alkalies, and can be reprecipitated from the solution by acidification[10,11]. It might be noted here that the present authors have found that some of the substituted rubeanic acids like *NN'*-dimethyl, -diethyl- and -diphenylrubeanic acids form colorless solution in caustic alkalies, but others like *NN'*-diisoamyl- and *NN'*-bis-(2-hydroxyethyl) rubeanic acids retain their colour unchanged in dilute alkali solution. Rubeanic acid itself also shows its usual colour in dilute aqueous alkalies. This suggests some unstable structural change predominating in the case of dimethyl, diethyl and diphenyl derivatives. It is likely to have some connection with the formation of aci- or semiaci- form of the substance (*vide infra*). In boiling concentrated caustic alkali solution rubeanic acid is decomposed with the formation of alkali sulphide, alkali cyanide, and alkali thiocyanate. When a solution in dilute aqueous alkali is boiled, it decomposes giving rise to alkali sulphide and alkali oxalate with liberation of ammonia[5]. In boiling dilute hydrochloric acid rubeanic acid suffers hydrolysis with formation of ammonium chloride, oxalic acid and hydrogen sulphide. Similar decomposition in hot alkalies and acids has also been reported for the *NN'*-disubstituted derivatives of rubeanic acid.

It has been observed by polarographic study that dithic-oxamide (rubeanic acid) in acid, basic, or neutral solution suffers reduction in two steps[20].

Rubeanic acid has been found to undergo condensation with mixtures of aldehydes and secondary amines[21]. It also suffers cyclization with α-halogen carbonyl compounds[22-25].

Rubeanic acid reacts with hydrazine to form the dihydrazone of oxamide with liberation of H_2S[26] and with hydroxylamine to yield oxalamidoxime[14].

TABLE II

Characteristic properties of metal rubeanates

Rubeanic acid=Rba. *NN'*-disubstituted derivatives: Dimethyl-, diethyl-bis- (2-hydroxyethyl)-, diisoamyl-, dibenzyl-, and diphenyl rubeanic acid=Me_2Rba, Et_2Rba, $(hydroxy\text{-}Et)_2$Rba, $(iso\text{-}Am)_2$Rba, Bz_2Rba, and Ph_2Rba respectively.

Metal	Rba (1)	Me_2Rba(2)	Et_2Rba(3)	$(Hydroxy\text{-}Et)_2$Rba(4)	$(iso\text{-}Am)_2$Rba (5)	Bz_2Rba (6)	Ph_2Rba (7)
Ag(I)	Yellow ppt., somewhat soluble in water	Orange-yellow ppt., decomposed by dil. acids and alkalies	Same as (2)	Yellow ppt., soluble in excess of alcohol	Same as (4)	Pale yellow ppt.	Yellow ppt., slightly soluble in organic solvents
Hg(I&II)	White ppt.	Same as (1)	Same as (1)	Same as (1)	Same as (1)		
Bi(III)	Yellowish brown ppt.						Yellow to brown ppt.
Pb(II)	Yellow ppt.	Same as (1)	Same as(1)	Same as(1)	Same as(1)	Yellowish white ppt.	Same as(1)
Cu(II)	Greenish black ppt., very sparingly soluble in pyridine, in butyln alcohol, ethyl or amyl acetate	Deep green ppt. with a blue tinge	Same as(2)	Dark green ppt. with a violet tinge, very sparingly soluble in benzene or toluene, soluble in pyridine with a greenish yellow soln; colour extractable with amyli or butyli alcohol	Dark green ppt. with a blue tinge, soluble in pyridine with a greenish yellow colour	Same as (1)	Soluble in pyridine with a greenish yellow colour extractable by amyli or butyli alcohol
Cd(II)	Yellow ppt.						Pale yellow ppt.
Fe(II)	Blue ppt.						
Zn(II)	White ppt.						

TABLE II (contd.)

Metal	Rba(1)	Me_2Rba(2)	Et_2Rba(3)	(Hydroxy-Et)$_2$Rba(4)	(iso-Am)$_2$Rba (5)	Bz_2Rba (6)	Ph_2Rba (7)
Co(II)	brown ppt., soluble in pyridine, giving orange-yellow soln. slightly soluble in amyl^i and butyl^n alcohol, acetone, ethyl and amyl acetate and in triethanolamine	Same as(1); colour of pyridine solution extractable by amyl^i or butyl^i alcohol, ethyl or amyl acetate and chloroform	Same as(2); colour of the pyridine soln. also extractable by benzene and toluene	Brownish yellow ppt., soluble in pyridine to give an orange-yellow soln. colour extractable by butyl^i or amyl^i alcohol, ethyl or amyl acetate	Dark brown ppt. fairly soluble in benzene, toluene, $CHCl_3$, CCl_4, amyl^i or butyl^i alcohol, ethyl or amyl acetate; soluble in pyridine with an orange-yellow colour extractable by the above solvents	Deep brown ppt., soluble in pyridine with an orange yellow colour extractable by toluene	Orange-brown ppt., sparingly soluble in acetone; easily soluble in benzene, toluene, chloroform, etc.; soluble in pyridine with an orange-yellow colour extractable by butyl^i or amyl^i alcohol
Ni(II)	Blue-violet ppt., dissolves in pyridine to a pink soln.	Red-violet ppt., otherwise same as (1); pyridine colour extractable by common solvents.	Purple-red ppt., otherwise same as (2)	Deep violet ppt., otherwise same as (2)	Same as(4); pyridine colour extractable by butyl^i or amyl^i alcohol, ethyl or amyl acetate	Deep violet ppt., fairly soluble in acetone, benzene, $CHCl_2$, butyl^i or, amyl^i alcohol, ethyl or amyl acetate; easily soluble in pyridine with a deep violet colour extractable by butyl or amyl^i alcohol, ethyl or amyl acetate, toluene and $CHCl_3$. Pyridine solution is unstable	Deep violet ppt., sparingly soluble in ethanol, acetone, butyl^i or amyl^i alcohol, ethyl or amyl acetate; easily soluble in pyridine with reddish pink colour extractable by butyl^i or amyl^i alcohol

TABLE II (contd.)

TABLE II (contd.)

Metal	Rba(1)	Me_2 Rba(2)	Et_2Rba (3)	(Hydroxy-Et)$_2$Rba(4)	(iso-Am)$_2$Rba (5)	Bz_2Rba (6)	Ph_2Rba (7)
Pd(II)	Red ppt., soluble in pyridine to give an orange-yellow soln., colour extractable by amyl^i alcohol; soluble in acetone, triethanolamine, amyl^i and butyl^n alcohol, ethyl and amyl acetate	Orange-yellow ppt., otherwise same as(1)	Same as (2)	Orange-red ppt., fairly soluble in ethanol, butyl^i and amyl^i alcohol, acetone; easily soluble in pyridine; pyridine colour extractable by amyl^i or butyl^i alcohol, ethyl or amyl acetate and $CHCl_3$	Deep red ppt., soluble in almost all common organic solvents; yellow colour of the pyridine soln. extractable by butyl^i or amyl^i alcohol	Orange-yellow ppt., soluble in acetone, chloroform, ethyl or amyl acetate and pyridine; yellow colour of pyridine soln. is extractable by toluene, benzene, etc. The solution in these solvents is rather unstable	Deep red ppt., soluble in most of the common organic solvents; the orange-yellow colour of the pyridine soln. is extractable by butyl^i or amyl^i alcohol, $CHCl_3$, CCl_4 and ethyl or amyl acetate
Au(III)	Orange ppt.	Yellow ppt.	Orange-yellow ppt.	Orange-yellow soln. giving a brown ppt. on standing	Golden yellow colour	Pale yellow ppt.	Orange-red ppt.
Ru (III & IV)	Blue ppt. giving a blue solution in strong acids	Same as (1)	Same as (1)	Same as (1)	Blue solution readily giving a blue ppt.		Greenish blue coloration, readily giving a ppt.
Pt(IV)	Rose-red	Yellow ppt.	Orange-brown ppt.	Orange-yellow soln. giving a brown ppt. on standing	Yellow ppt.	Orange-yellow coloration	Brownish red unstable ppt.
Tl(I)	Yellow ppt.						

With benzaldehyde rubeanic acid reacts to produce a thiazolo-thiazole derivative[27,28].

With many metal ions in solution rubeanic acid and its derivatives react to form intensely coloured insoluble precipitates[2,14,29-37].

Almost all metal ions, which give precipitates with sulphide ion in acid, neutral, or alkaline solution, are precipitated by rubeanic acid and its derivatives* (disubstituted). The colour and properties of these metal compounds of rubeanic acid and some of its derivatives, are recorded in Table II, mainly from the observation of Rây and Ray and of Xavier and Rây[37].

The solubility values of copper (II), nickel (II) and cobalt (II) rubeanates in neutral, alkaline, and acid solutions, as determined by Malyuga[38] along with the values of their solubility products in water given by the same author, are quoted in Table IIA.

TABLE IIA

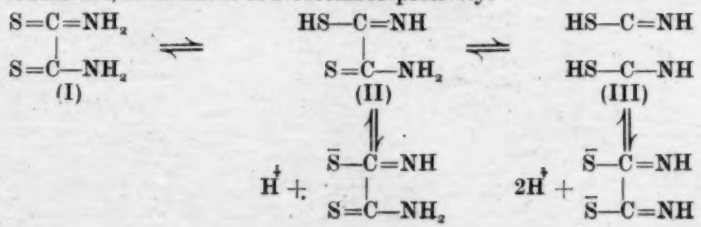
Metal	Solubility product	Solubility (in moles per litre) at 18° in Water	0.01*M* aq. NH_3	Soln. containing 0.1*M*-NH_4 Cl, 0.010*M*, NaOH & 0.1*M* citric acid	0.001*M* HCl
Copper	7.67×10^{-16}	5.8×10^{-8}	7.7×10^{-7}	6.8×10^{-8}	3.0×10^{-7}
Nickel	1.1×10^{-15}	7.2×10^{-8}	7.6×10^{-7}	7.5×10^{-8}	1.1×10^{-6}
Cobalt	1.2×10^{-15}	7.4×10^{-8}	9.0×10^{-7}	5.4×10^{-8}	6.7×10^{-7}

Compounds of rubeanic acid with Fe(II), Au(III), Pt(IV), Hg(I & II), Bi(III), Pb(II), Cd(II) and Tl(I) are all unstable, decomposing more or less into the corresponding sulphide. Copper, nickel and cobalt are precpitated quantitatively from slightly acid or ammoniacal solution; silver and thallium from neutral solution; iron, lead and cadimum from neutral or alkaline solution; mercury, bismuth, palladium, gold, platinum and ruthenium from acid solution. In an excess of mineral acids ruthenium gives a blue solution.

A consideration of the properties of metal rubeanates, as recorded in Table II, shows that *NN'*-disubstituted derivatives of rubeanic acid differ but little in their reaction with metal ions from their parent body (rubeanic acid), except in a gradual change in the colour shade and solubility of the product with the nature and size of the substituent. On the other hand, it has been found that a tetra-substituted derivative, tetraethylrubeanic acid, fails to give any characteristic reaction with metal ions[32,38], due obviously to the absence of any hydrogen atom available for salt formation.

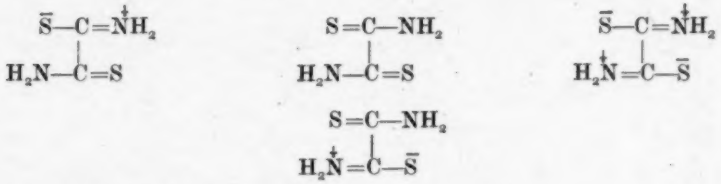
Structure

Rubeanic acid is identified with dithio-oxamide as it results from the sulphhydrolysis of cyanogen, in analogy with the formation of oxamide from cyanogen by hydrolysis. In solution it is likely to occur therefore as an equilibrium mixture of the tautomeric thione (I), thione-thiol (II) and thiol (III) forms, denominated otherwise as diamido or base, amid-imido or semi-aci, and diimido or aci forms respectively.



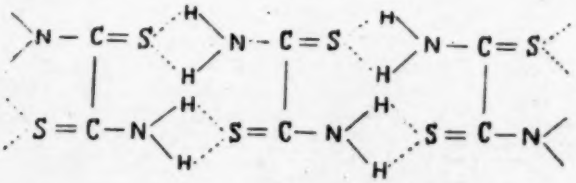
In addition, a dissociation equilibrium for II and III, however small, must also be taken into account, which is responsible for its salt-forming or acid character. Moreover, all these forms may again occur in their corresponding isomeric *trans* or *anti*-configuration. Each of these forms of the *cis* or *trans* type may further resonate among several valence bond structures on account of conjugation in the molecule[3,39].

The X-ray diffraction study of single crystals of rubeanic acid by Long *et al.*[18] shows that each unit cell contains two planar molecules, each lying on a centre of symmetry and that C-C bond length corresponds to that for a single bond, while C-N and C-S distances partake of double bond character. The results are indicative of a *trans* configuration of the molecule resonating among the structures like:



In solution, when the crystal structure is destroyed, the molecule may, however, assume partially a *cis* configuration as well, besides tautomerising into thione-thiol and thiol forms.

On the basis of his study of the infrared absorption spectra of rubeanic acid Barcelo[19] has assigned a chain-like polymeric formula IV for the compound, representing it as a body of associated molecules.



(IV)

The structure suggested is based primarily on a comparison of the N-H stretching frequencies of the rubeanic acid with those of *N*-methylacetamide in the region of 3,000-3,400 cm^{-1}. No direct evidence from the spectra of rubeanic acid itself may be said to have been furnished. Moreover, the X-ray spectra of rubeanic acid provide no indication of such a chain-like polymeric structure for the substance (cf. Long *et al.*)[18].

No evidence has yet been reported, however, about the association of rubeanic acid molecules in solution in any solvent.

Metal Rubeanates

(*a*) *Preparation and Properties*—Copper (II), nickel (II) and cobalt (II) rubeanates were described by Rây and Ray[2].

When an alcoholic solution of rubeanic acid is added to a slight excess of copper sulphate solution, copper rubeanate is precipitated as a voluminous slimy greenish black

mass, which after washing and drying changes to black shining scales. The composition, based on the analysis of the dry product, corresponds more closely with $Cu(C_2S_2N_2H_2).0.5H_2O$ than with the anhydrous body. When heated above 160° the compound decomposes. It dissolves with decomposition in moderately strong boiling hydrochloric acid, and is decomposed by boiling caustic alkali with formation of copper sulphide, alkali cyanide and sulphocyanide.

Nickel rubeanate is obtained as a bluish violet slimy precipitate in a similar manner from an aqueous solution of nickel salt; but no precipitation occurs unless the solution is rendered alkaline with sodium acetate or dilute ammonia. In presence of strong ammonia an intense red product separates, changing readily into the bluish violet compound. The compound shows the composition $Ni(C_2S_2N_2H_2)$. It resembles the copper rubeanate in properties, but dissolves partially in 8% ammonia to form a bluish violet solution and forms a deep orange-red solution in stronger ammonia. In caustic alkali it dissolves to a yellowish red solution, which turns pink when diluted. From this solution the bluish violet nickel rubeanate is reprecipitated by neutralization.

Nickel (II) compounds of some substituted rubeanic acids, viz., *NN'*- dimethyl (I), -dibenzyl (II),-dioctadecyl (III), -bis-(2-hydroxyethyl) (IV),-bis-(2-acetoxyethyl) (V), and -bis-(3-dimethylaminopropyl) rubeanic acid, have been recently described by Hurd *et al.*[38] They can be represented by the general formula: $[Ni(RNSCCSNR)]_n$, where $R=C_6H_5CH_2$, $C_{18}H_{37}$, HOH_2CCH_2,$CH_2COOCH_2CH_2$ and $(CH_3)_2NCH_2CH_2CH_2$.

With dimethylrubeanic acid nickel, however, showed variable composition depending on the manner of its preparation and purification. When prepared in the absence of any base in aqueous alcoholic solution, the composition of the product obtained is represented by the authors as (DMR) $[(Ni(DMR\text{-}2H)]_4$ Ni(DMR); where $DMR=CH_3HNSCCSNHCH_3$ and $DMR-2H=CH_3NSCCSNCH_3$. When prepared in the presence of an alkali the products cantained sodium in addition. These have been represented by the composition: $[(DMR\text{-}2H)Ni)]_{6\text{-}8}$ (DMR-H)Na and Na (DMR-H) $[(DMR\text{-}2H)Ni)]_{18}$ (DMR-H)Na. All these compounds were regarded as more or less highly polymerised, the value of *n* being quite high.

With ammonia, methylamine, triisopropanolamine, di-(aminopropyl)amine, ethylenediamine and *o*-phenanthroline, nickel(II) rubeanate and Ni(II) *NN'*-dimethylrubeanate are reported to form insoluble products of intense purple, blood-red, dark red or red-brown colour[14].

All the nickel (II) rubeanates that have been described are highly coloured solids of various shades of blue, violet and purple. The nickel(II) dimethylrubeanate is crystalline and paramagnetic (B.M.=2.4.).

Cobalt rubeanate is obtained as a reddish brown hygroscopic powder from a cobalt salt solution and rubeanic acid in presence of sodium acetate or ammonia. It has the composition $Co(C_2S_2N_2H_2).2H_2O$ and resembles the nickel rubeanate in properties.

By the action of an aqueous alcholic solution of rubeanic acid on an ammoniacal solution of carbonatotetramminecobaltic nitrate a dull brown insoluble cobalt (III) rubeanate of the composition, $Co_2(C_2S_2N_2H_2)_3(NH_3)_2H_2O$, has been obtained; this on drying at 115°-120° loses $2H_2O$[2]. The occurrence of cobalt (III) rubeanate as $Co_2(C_2N_2H_2)_3$ in solution at *p*H 9 in presence of a protective colloid like gum acacia, which serves to keep the compound in solution, has been demonstrated by Jacobs and Yoe[40] by spectrophotometric measurements following three independent methods: the mole ratio method of Yoe and Jones[41], continuous variation method of Job as modified by Vosburg and Cooper[42], and the slope

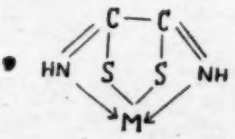
ratio method of Harvey and Manning[43]. It appears therefore that in alkaline solution cobalt (II) rubeanate is oxidized to the cobalt (III) compound. Alike spectrophotometric measurements on copper (II) and nickel (II) rubeanates in solution containing gum acacia have confirmed their empirical composition with 1 mole ion of copper or nickel for 1 mole of the reagent[40]. These observations have also been confirmed by the same authors[44] using a derivative of rubeanic acid as well, namely, *NN''*-bis-(3-dimethylaminopropyl) rubeanic acid. The same conclusion regarding the composition of copper rubeanate was arrived at previously from physico-chemical studies of the copper rubeanic acid system by Tananaev and Levitman[45].

Palladium has been found to combine with rubeanic acid to afford a number of compounds having the composition Pd_3Rba_2, PdRba, Pd_2Rba_3 and $PdRba_2$ (where Rba = a rubeanic acid molecule or its radical), depending on the *p*H value of the medium during precipitation and the amount of the reagent present. Compositions of these compounds were determined both by heterometric titration of palladium chloride solution with rubeanic acid as well as by microanalysis of the dried products[46]. A compound of the composition, $Pd(C_2S_2N_2H_2)_2 \cdot 2C_2S_2N_2H_4$, also was described by Wolbling and Steiger[32]. In this the reagent is supposed to react in its semi-aci form.

Spectrophotometric measurement of the optical density of the blue coloured solutions derived from ruthenium salts and rubeanic acid has shown that both Ru (III) and Ru (IV) form the same complexes. $[RuSC(NH)CSNH_2)^{2+}$ and $Ru[SC(NH)CSNH_2]_3$; in these the reagent seems to react in its semi-aci form[47]. The formation constants of the compounds have also been determined by these authors.

The formation of gold rubeanates of composition, Au_3Rba_2, AuRba and $AuRba_3$, analogous to those of palladium, has also been established by Bobtelsky and Eisentadter[46] by heterometric titration and analysis as with palladium. A gold compound of the composition, $[Au(C_2H_5)_2]_2\ C_2S_2N_2H_2$, has also been described[48].

(*b*) *Structure*.—Rây and Ray were the first to suggest that rubeanic acid reacts with metal ions in its aci or dithiol form, giving rise to inner metal complexes, as it can then offer both salt-forming (-SH) and coordinating (=NH) groups. The structure V with two interpenetrating 5-membered rings was proposed by them for the rubeanates of copper (II), nickel (II) and cobalt (II).

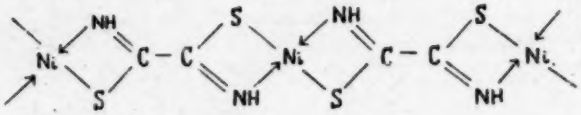


where M=Cu(II), Ni(II) or Co (II).

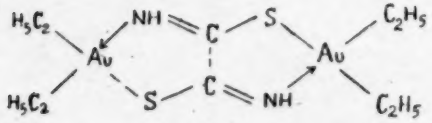
As the nickel complex was found to be diamagnetic[49] it must be assumed that the metal atom should be linked to the sulphur and nitrogen atoms in a square planar configuration[50]. But this is likely to involve a considerable strain in the molecule, rendering it unstable. In analogy with some tetracoordinated, diamagnetic nickel mercaptides, which were known to be polymers, Jensen[51] suggested that nickel (II) rubeanate must also be formulated by a polymeric structure VI in the form of a chain.

Ewens and Gibson[52] have described a binuclear gold rubeanate, tetraethyldigold rubeanate, whose structure is represented by them by the configuration VII resembling

that of the nonelectrolyte (2-aminoethylthio) diethylgold studied by them. In this latter the sulphur atom has been found to display the reactivity typical of an organic sulphide. This illustrates the bridging capacity of the rubeanic acid molecule as well as its occurrence in the *trans* form in complex formation. The structure VII postulated by

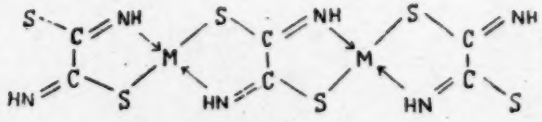


(VI)



(VII)

Ewens and Gibson for metal rubeanates involves the formation of 5-membered rings and, for this reason, is preferable to that of Jensen with 4-membered rings which are not likely to contribute to the stability of the complex formed. The structures of copper (II), nickel (II), cobalt (II) and palladium (II) complexes of rubeanic acid are therefore best represented by a chain like polymeric structure VIII.

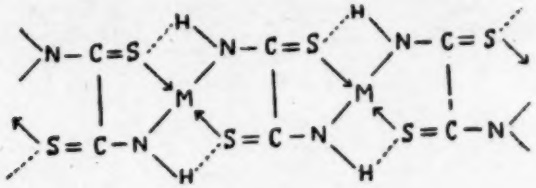


(VIII)

This assumption of the chain-like polymeric structure for the metal rubeanates has been strengthened by the work of Amon and Kane[53] who found that when a plastic sheet covered with the precipitate of metal rubeanic acid complex was stretched in one direction, the polymer chains were oriented parallel to each other; for, the polarisation of transmitted light could not be accounted for in any other way.

In the case of gold rubeanic acid complexes with gold in the tervalent state, an octahedral coordination for the metal atom should be assumed in order to satisfy its valency. This would necessitate the formation of a sheet like structure on polymerisation.

Recently Barcelo[19] from a study of the infrared absorption bands of copper (II), nickel (II) and cobalt (II) rubeanates has suggested the structure IX for these compounds



(IX)

In this the rubeanic acid molecule is represented to react in its thionic form with the amido ($-NH_2$) group exercising the acid function, for which, however, there is little or no justification. Evidences furnished by the infrared spectra are also inadequate to warrant the above representation, as already stated in discussing the structure of rubeanic acid itself. The argument advanced in favour of this structure by Hurd *et al.*[38] that *NN'*-tetraethylrubeanic acid that contains no amido hydrogen does not react with Ni(II) ion in aqueous alcoholic solution carries little conviction. For, this only shows the absence of any hydrogen atom available for giving rise to the thio-enolic configuration responsible for complex formation.

It is curious to note that whereas nickel (II) rubeanate is diamagnetic like nickel (II) mercaptides, nickel (II) dimethylrubeanate has been found by Hurd *et al.*[38] to show paramagnetism with a moment value of 2.4 B.M. It seems not unlikely that the fairly drastic treatment to which it was subjected at a more or less elevated temperature during its purification produced a change in its structure from the square planar configuration to that of tetrahedral or octahedral type.

Uses

(*a*) *Detection of Metals.*—Rubeanic acid, and recently many of its derivatives, have been extensively investigated for use as an analytical reagent, particularly for the detection and determination of trace amounts of Cu, Ni, Co, Pd, Ru and Ag (cf. Wenger and Duckert—Editors, Reagents for Qualitative Analysis, Elsevier Publishing Co. Inc., New York, 1948.; Welcher, Organic Analytical Reagents Vol. IV, Van Nostrand Co. Inc., New York, 1948).

First introduced by Rây and Ray[2] for the micro-detection of Cu, Ni and Co, the scope of applicability of rubeanic acid as a reagent in chemical analysis has widened considerably through the work of various investigators. Early studies were centred more or less on specifying the identification limits of individual metals and on interferences in their detection. The identification limits for the above mentioned metals by spot tests with rubeanic acid and some of its derivatives are given in Table 3 which also includes the limits by thread and capillary tests with the parent reagent.

A complete qualitative separation of a small amount of copper from a large amount of cadmium in presence of dilute sulphuric or acetic acid by rubeanic acid, using microchemical method, has been also reported by Rây[3].

Capillary separation of copper from nickel or cobalt on filter paper by means of rubeanic acid, which produces a central spot of olive-green copper rubeanate surrounded by a blue zone of nickel or a brown zone of cobalt precipitate, has been described by Feigl and

Kapulitzas[45]. A disc chromatographic method of detecting all the three metals simultaneously has been developed by Pollard and McOmie[55]. Rubeanic acid is used here as a developer[56].

TABLE III

[R=Rubeanic acid, DMR=Dimethylrubeanic acid, DER=Diethylrubeanic acid, DHxER=Di-(hydroxyethyl) rubeanic acid, DIAR=Diisoamylrubeanic acid, DBR=Dibenzylrubeanic acid, DPhR=Diphenylrubeanic acid].

Reagent	Identification limits (μg)					Reference
	Copper	Nickel	Cobalt	Palladium	Ruthenium	
R	0.012	0.006	0.030		0.20	3,32
	0.006	0.012	0.030			57
	0.002	0.0002	0.906			3 (thread test)
	0.002	0.006	0.002			3 (capillary test)
DMR	0.180	0.040	0.025	0.067		37
DER	,,	,,	,,	,,		37
DHxER	0.050	0.015	0.025	0.060		37
DIAR	0.050	0.020	0.030	0.100		37
DBR	0.100	0.040	0.035	0.060		37
DPhR	0.100	0.400	0.100	0.200	0.060	37

Using malonic acid and ethylenediamine as sequestering agent for interfering ions West[58] has utilized rubeanic acid as a specific spot-test reagent for copper. The same author[59] has demonstrated a fascinating test in which 10^{-9} μg of copper can be detected by means of rubeanic acid in human skin. The reagent has also been used for the detection of copper and nickel in steel[59a].

Thomson[60] has reported the detection of 0.002 μg of cobalt at a dilution of 1:1,000,000 by means of coloroscopic method.

Dubsky, Okac and Tritlek[61] reported detection of bismuth with an acid solution of rubeanic acid, which could not be confirmed[34].

Conditions for the detection of nickel on the surface of an ion-exchange resin with rubeanic acid have been investigated by Fujimoto[62]. The sensitivity is 0.0021 μg of Ni at a limiting concentration of 1 in 1.9×10^7.

(*b*) *Determination of Metals.*—Rubeanic acid was first employed by Rây and Ray (loc. cit.) for the quantitative precipitation of copper, nickel and cobalt from ammoniacal solution. Since then it has been studied by several investigators for use as a colorimetric reagent for the determination of a number of transition metals, primarily of copper. Recently attention has been directed to some of its derivatives also, which have proved to be quite useful for the purpose and even to possess special advantages in some cases.

Using protective colloids such as gelatine or gum acacia copper has been determined colorimetrically from the measurement of the intensity of its greenish black colour[63,64,40]. A buffer solution of ammonium acetate+acetic acid or malonic acid (pH=4) has also been employed for the purpose in place of a protective colloid[65]. Copper has been determined

by these means in steel, alloys and other products by various workers[66]. Measurements were made spectrophotometrically by some of the later workers. Tartrate, citrate and malonic acid were used to sequester interfering ions.

Jacobs and Yoe[40,44,67] used 8 different derivatives of rubeanic acid besides rubeanic acid itself for the spectrophotometric determination of copper using gum acacia as the protective colloid. Xavier and Rây[37] employed *NN'*-di-(2-hydroxyethyl) rubeanic acid and *NN'*- diphenylrubeanic acid in acetone-pyridine and aqueous pyridine solution respectively for the same purpose, as copper complexes of these two derivatives were found to be fairly soluble in pyridine. With *NN'*-diphenylrubeanic acid copper was determined in aqueous pyridine in this manner in presence of several interfering ions like Co^{2+}, Ni^{2+}, Pb^{2+}, Cd^{2+}, Cr^{3+}, Sn^{2+}, MoO_4^{2-}, and WO_4^{2-} using disodium versenate (ethylenediaminetetraacetate) as a masking agent. In the case of *NN'*-di(2-hydroxyethyl) rubeanic acid the colour of the copper complex in pyridine was also partially masked. Table IV gives the wave lengths of absorbance maximum, molar extinction coefficients and sensitivities of the coloured copper complexes studied. It would appear from this table that the values of sensitivity and molar extinction coefficient are much higher with protective colloids than in pyridine solution. But it might be pointed out that the coloured complex of copper (II) *NN'*-di (2-hydroxyethyl) rubeanic acid and of copper (II) *NN'*-diphenylrubeanic acid can be extracted out from their pyridine solutions by butyl^i or amyl^i alcohol, whereby the method of estimation might be further refined and made more sensitive.

TABLE IV

Copper (II) *complexes*

NN'-bis or di-(carboxymethyl) rubeanic acid, $HOOCH_2NHSCCSNHCH_2COOH$=DCxMR; *NN'*-bis-(2-sulphoethyl) rubeanic acid, disodium salt, $NaSO_3CH_2CH_2NHSCCSNHCH_2CH_2SO_3Na$=DSER ; *NN'*bis-(3dimethylaminopropyl) rubeanic acid, $(CH_3)_2NCH_2CH_2NHSCCSNHCH_2CH_2N(CH_3)_2$=dDMAPR.; *NN'*-bis-(3-methoxypropyl) rubeanic acid, $CH_3O(CH_2)_3NHSCCSNH(CH_2)_3OCH_3$=DMX PR; *NN'*-Dicyclohexylrubeanic acid, $C_6H_{11}NHSCCSNHC_6H_{11}$=DcHR; *NN'*-didodecylrubeanic acid, $CH_3(CH_2)_{11}NHSCCSNH(CH_2)_{11}CH_3$=DdDR; other symbols have the same significance as in Table III.

Reagent	$\lambda_{max.}$	Mol. extinc. coeff.	Sensitivity (γ/cm^2)	Reference
R	385 mμ	15,800	0.0037 (Sandell) 0.0190 (practical)	40, 67
DER	365	12,900	0.0050(S)	40, 67
DCxMR	340	6,030	0.0150(S)	40, 67
DHxER	380	15,600	0.0040(S)	40, 67
DHxER in pyridine soln.	390 (measured at)	8,800	0.0070(S) 0.0300(p)	37
DSER	380	12,900	0.0050(S)	40, 67
dDMAPR	365	15,000	0.0040(S)	40, 67
DMxPR	380	15,700	0.0040(S)	40, 67
DcHR	385	10,400	0.0060(S)	40, 67
DdDR	385	26,700	0.0020(S)	40, 67
DPhR (pyridine soln.)	420	6,060	0.0100(S) 0.0800(P)	37

Amperometric and complexometric titration methods for estimating copper by rubeanic acid have also been reported by some authors[68].

Nickel and cobalt have also been determined spectrophotometrically by Jacobs and Yoe[40] as well as by Xavier and Rây[37] using rubeanic acid and a number of its *NN'*-disubstituted derivatives. The first named authors employed gum acacia to maintain the coloured complexes in solution and the latter used the alcoholic or aqueous pyridine solution. The values of λmax, molar extinction coefficient (ε) and sensitivity in γ/cm^2 for the coloured species are listed in Table V.

TABLE V

Cobalt and nickel complexes

[Symbols for the reagents have the same significance as in Table IV]

Reagent	Cobalt			Nickel			Reference
	λmax.	ε	Sensitivity	λmax.	ε	Sensitivity	
R	370	13,000	0.0040(S) 0.0200(p)	640	8,930	0.0070(S) 0.0340(p)	40
	400	13,800	0.0040(S) 0.0100(p)	530	5,900	0.0100(S) 0.0400(p)	37
DMR	395	14,€00	0.0040(S) 0.0250(p)	485	7,900	0.0075(S) 0.0300(p)	37
DER	395	14,200	0.0045(S) 0.0300(p)	490	7,500	0.0080(S) 0.0300(p)	37
	350	13,600	0.0040(S)	510	5,570	0.0110(S)	40
DiAR	390	10,600	0.0056(S) 0.0300(P)	510	8,170	0.0070(S) 0.0300(P)	37
DHxER	400	10,000	0.0060(S)	490	4,980	0.0180(S)	40
DCxMR	400	12,700	0.0050(S)	345	6,900	0.0090(S)	40
DSER	345	5,900	0.0100(S)	510	4,100	0.0140(S)	40
dDMAPR	350	14,800	0.0040(S) 0.0250(p)	500	7,150	0.0080(S) 0.0390(p)	40
DMxPR	345	18,500	0.0030(S)	510	6,150	0.0090(S)	40
DcHR	380	8,800	0.0070(S)	520	5,900	0.0100(S)	40
DdDR	400	16,800	0.0040(S)	525	11,400	0.0070(S)	40
DPhR	410 (measured at)	18,300	0.0030(S) 0.0250(p)	510	8,000	0.0075(S) 0.0300(p)	37

S—Sandell, p=practical.

The spectrophotometric determination of cobalt in pyridine solution can be carried out in the presence of a moderate amount of nickel (using KCN as the masking agent),

copper and silver (using thiourea) and of iron (III) using fluoride. Interference by copper in moderate amount is also eliminated by the addition of KCN[37,40].

Jacobs and Yoe[40] have described a method for the simultaneous spectrophotometric determination of cobalt, nickel and copper in the same solution (using) rubeanic acid and *NN'*-bis-(3-dimethylaminopropyl) rubeanic acid in presence of gum acacia. The method is based on the use of the values of extinction coefficients of the coloured complexes of the three metals at the optimum wave lengths of their absorbance for deriving equations for the determination of one or more components. Results of analysis of several synthetic and standard samples by this method have also been reported by the authors.

Palladium is precipitated quantitatively by rubeanic acid at *p*H 3[69]. The precipitate is soluble in pyridine giving an intense orange-yellow solution. The metal has been estimated spectrophotometrically by rubeanic acid in alcoholic pyridine medium. By the addition of sodium versenate followed by the extraction of the coloured species by isoamyl alcohol interference due to Cu(II), Ni(II), Co(II), Cd(II), Fe(III), etc. can be eliminated, but Pt(IV), Au (III) and Ag (I) would interfere[37]. Xavier and Rây[37] have also employed dimethyl, diethyl and diphenylrubeanic acids for the estimation of palladium by spectrophotometric method in alcoholic or aqueous pyridine medium. With bis-(2-hydroxyethyl) and diisoamylrubeanic acids, however, pyridine was found to be unsuitable, as the colour did not fully develop in alkaline medium. In their case palladium was estimated in alcoholic solution[37].

The values for the wave length of absorbance maximum or optimum absorbance, the molar extinction coefficient and the sensitivity of coloured palladium complexes of rubeanic acid and some of its derivatives are recorded in Table VI.

The blue colour developed by ruthenium in strong hydrochloric acid solution with rubeanic acid and its derivatives has been utilized for its determination by spectrophotometric measurement[69a,37]. Rubeanic acid and its dimethyl, diethyl and bis-(2-hydroxyethyl) derivatives all give maximum absorbance in the region of 610-670 mμ. They all show practically the same sensitivity of 0.01 γ cm² (S) and 0.04 γ/cm²(p) with a molar extinction coefficient of 5,200 for rubeanic and bis-(2-hydroxyethylrubeanic acids, and of 5,800 for dimethyl and diethylrubeanic acids. Osmium has been found to interfere in the determination.

TABLE VI

Palladium complexes.

Reagent.	$\lambda_{max.}$	Molar extinc. coeff.	Senstitivity (γ/cm²)
Rubeanic acid (Rba)	410	4,600	0.0130 (Sandell) 0.0500 (practical)
Dimethyl-Rba	395 (op.)	4,080	0.0140 (S) 0.0500 (p)
Diethyl-Rba	395	4,680	0.0140 (S) 0.0500 (p)
Bis-(2-hydroxyethyl)-Rba	390	5,520	0.0110 (S) 0.0500 (p)
Diisoamyl-Rba	395	5,790	0.0110 (S) 0.0400 (p)
Diphenyl-Rba	395	7,920	0.0075 (S) 0.0250 (p)

Silver has been determined spectrophotometrically from the yellowish brown colour which it develops by treatment with rubeanic acid in aqueous solution[37]. Measurements were made at 390 mμ at *p*H 4.0-4.6. It gives a practical sensitivity value of 0.05 $\gamma Ag/cm^2$.

A comparison of the wave lengths of maximum absorbance and sensitivity values of coloured complexes of the metals with rubeanic acid and its various derivatives shows that no significant chromotropic effect is obtained by mono-substitution of alkyl or aryl groups at the two ends of the parent ligand, except an appreciable shift in the case of the nickel complex from 460 mμ to 500 mμ region and even to about 350mμ for the nickel complex of *NN'*-bis-(carboxymethyl) rubeanic acid. There is also no marked difference in sensitivity observed as the result of substitution.

From the spectrophotometric measurement at 625 mμ of the absorbance of light reflected by the blue-violet spot of nickel (II) rubeanate on a filter paper a method for the microchemical determination of nickel in quantitative chromatography has been described by Vaeck[70].

A turbidimetric titration method for cobalt by rubeanic acid in solution containing gum acacia has been developed by Tananaev and Shapiro[71]. Incidentally the authors have confirmed the composition of cobaltic rubeanate as $Co_2(C_2S_2N_2H_2)_3$.

(*c*) *Miscellaneous Applications.*—A number of new and quite interesting applications of rubeanic acid and its derivatives in the field of arts and industries has been suggested particularly in recent times. This has widened the scope of investigation on this remarkable reagent and its derivatives, whose number is increasing rapidly with time.

An application of rubeanic acid was suggested somewhat earlier by Nilsson[72] for toning or intensifying photographic images.

The antibacterial action of rubeanic acid and its effectiveness, when present in very low concentration of 10 mg per cent, against certain organisms like staphylococci has been recently investigated[73]. Several *NN'*-disubstituted rubeanic acids have been found similarly effective in inhibiting staphylococci, E. coli, pleuropneumonia-like organisms and tuberculi bacilli[74].

Rubeanic acid and many of its disubstituted derivatives have been found effective as metal deactivators in petroleum products, when employed in concentration of 0.001 to 1% by weight[75].

The autoxidation of cyclohexane catalysed by the presence of copper (II) is retarded by the use of *NN'*-dicyclohexylrubeanic acid which masks the activity of copper[76].

Rubeanic acid has been found to be quite effective in removing copper (II) turbidity from wine and is preferable to potassium ferrocyanide which is commonly used for the purpose[77].

Metal complexes of rubeanic acid and its derivatives have been suggested for use as pigments.

Mixed with a fusible metal soap, rubeanic acid and its derivatives have been employed in thermal duplicating processes[78]. The usefulness of these reagents in electrochemical reproduction has also been suggested (Mallinckrodt, loc. cit.)

Some *NN'*-disubstituted rubeanic acids have been found useful as vulcanization accelerators[79].

NN'--Dibutylrubeanic acid has been found to produce complete defoliation of mature

cotton[80]. Rubeanic acid and many of its disubstituted aliphatic derivatives have been found to inhibit the germination of some grass seeds, and to retard the growth of various seeds and grasses[14].

Rubeanic acid and many of its drivatives have been found useful as rodent repellent while *NN'*-didodecylrubeanic acid has been reported to possess activity as a bird repellent[81].

Rubeanic acid and its derivatives have been used in organic preparations for the synthesis of a wide variety of heterocyclic compounds.

It is hoped that this review will be found helpful to those who are interested in this new series of reagents which hold promise of such a wide variety of applications.

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Latent Heat of Evaporation, Density, Temperature, and Composition of Organic Liquids

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The correlation of the structure of organic molecules with their physical properties has been a coveted aim of chemists for a long time. Molecular volume, being one of such physical properties, was seriously studied from an early time. Molecular volumes based on density, measured near the boiling point, were extensively investigated by Kopp[1], Traube[2], and Le Bas[3]. Definite quantitative relationships were observed and atomic values were derived to be used in an additive manner. These values have been useful in spite of certain obstacles, the greatest of which has been the difficulty, if not the impossibility, of comparing molecules in the same or corresponding states. One effort to overcome this difficulty led to the determination of the so-called "Nullpunkt's Volume", which was obtained by the extrapolation of temperature-density curves to absolute zero, by Biltz, Fischer, and Wunneberg[4]. Another promising approach was based upon Guldberg's[5] rule. Since the boiling point of a substance is approximately two-thirds of its critical pressure, molecular volumes have been compared at temperatures which are some constant fraction of the boiling point. These theoretical modifications of the simple molecular volume concept have been somewhat disappointing in the final analysis.

The most successful attempt in this direction has been the concept of *parachor* by Sugden[6] based upon the empirical relationship discovered by Macleod[7] between surface tension and density, and theoretically deduced by Fowler[8]. The parachor gives us a method to compare the molecular volumes of different compounds at the temperature of unit surface tension. This parachor has been found to possess primarily an additive property, the parachor of a compound being the sum of the atomic parachors, with some additional terms where certain structures, such as double and triple bonds and cyclic structures, are present. The chief significance to be attached to a comparison of molecular volumes at constant surface tension instead of at constant temperature, or at a reduced temperature, e.g., the boiling point, is that this method does make some allowance for the effect on molecular volumes of the forces due to molecular attractions. The comparison of parachor with critical volume and mean collision area supplies further evidence for the view that parachor is a true measure of the molecular volume. Mumford and Philips[9], Vogel[10], Quayle *et al*[11]. and Gibling[12] have detected certain shortcomings in Sugden's attractively simple treatment of the parachor as an additive function and modified the values of atomic parachors.

Because of the relationship observed between the parachor and several other properties, other derived properties related to the parachor have been suggested. Bogdan[13] has suggested the *neoparachor*, which is a function of the molecular volume and the absolute boiling point. Friend and Hargreaves[14] have suggested *rheochor* which is a function of vis-

cosity and molecular volume. Bowden and Jones[15] suggested the *lyoparachor*, which is a function of the internal latent heat of vaporisation and density of a liquid. This was based on the empirical relation found by them among internal latent heat of vaporisation (λ_i), the density of the liquid (D), and the orthobaric density of the vapour (d) at a particular temperature:

$$(\lambda_i = K(D-d)^{4/3}$$

where K is independent of temperature over a wide range,

$$\therefore \quad \frac{\lambda_i^{3/4}}{D-d} = K$$

Multiplying each side by the molecular weight of the liquid (M)

$$\frac{M.\ \lambda_i^{3/4}}{D-d} = MK = \text{lyoparachor } (\lambda).$$

It is not the purpose of the present paper to criticise the work of Bowden and Jones[15] but the same relationship was found by the author[16] in 1926.

These relationship are as:

$$\lambda_i = K\ (D-d)^{3/2} \qquad .. \qquad .. \qquad (i)$$

$$\lambda = K_1\ (T_c - T)^{0.45} \qquad .. \qquad .. \qquad (ii)$$

$$D-d = K_2\ (T_c - T)^{0.3} \qquad .. \qquad .. \qquad (iii)$$

where λ_i=internal latent heat of vaporisation, T_c=absolute critical temperature, T=the absolute temperature, D and d are the densities of the liquid and its orthobaric vapour at the corresponding temperature T. Tables I, II, and III show the application of these empirical equations (*i*), (*ii*), and (*iii*) over a wide range of temperature, showing the constancy of K, K_1 and K_2.

TABLE I

Values of K at different temperatures for various liquids.

Compounds.	0°.	20°.	40°.	60°.	80°.	100°.	120°.	140°.	160°.	200°.
Benzene	23.80			24.00	24.0	23.90				
Carbon tetrachloride	8.13			8.14	8.14	8.12				8.10
Diethyl ether	26.3	26.2	25.9	25.7		25.7	25.9			
Isopentane	29.2	29.1	28.8	28.7						
Pentane[n]	29.6	29.6	29.6	29.7						
Hexane[n]	28.1		28.1	28.1	28.2					
Ethyl formate	22.7	22.7	22.7	22.6	22.7					
Ethyl acetate	22.4			22.2	22.2	22.2				
Tin tetrachloride						4.7	4.7	4.7	4.6	4.6
Methanol	51.9			52.4	52.3	51.8				
Ethanol	43.7		45.1	45.2	45.6	45.0	44.8	45.3		

TABLE II

Values of K_1 at different temperatures for various liquids.

Compound.	0°.	20°.	30°.	40°.	60°.	70°.	100°.	110°.	120°.	200°.	280°.
Ethyl acetate	7.84	7.67			7.67	7.69	7.71				
Diethyl ether	7.94	7.88	7.73	7.68			7.66		7.56		
Benzene	7.74				7.79	7.81	7.74				
CCl_4	3.79					3.78	3.79		3.79	3.71	
Tin tetra-chloride							2.56	2,55	2.49	2.45	2,52

TABLE III

Values of K_2 at different temperatures for various liquids.

Compound.	0°.	20°.	80°.	120°.	140°.	150°.	160°	200°.	250°.	280°.	300°.
Ethyl acetate		5.69	5.70	5.70			5.71	5.78			
Chlorobenzene						5.21	5.20	5.20	5.22		5.30
Benzene	6.08		6.12	6.11		6.13		6.14			
Diethyl ether	6.61	6.60	6.62	6.60	6.59	6.71					
CCl_4	3.32	3.34	3.35	3.35		3.36		3.37			
Methyl formate	4.99	4.99	5.30			5.05					
Tin tetra-chloride			2.50	2.50		2.50		2.51		2.61	

If equation (*i*) is multiplied by the molecular weight (M) of the substance,

$$\frac{M}{D-d} \times \lambda_i^{2/3} = M \times K$$

At low temperature, d is very small and can be neglected.

$$\therefore \quad \frac{M}{D} \times \lambda_i^{2/3} = M \times K$$

$$\therefore \quad \text{Molecular volume } (V_m) \times \lambda_i^{2/3} = M \times K$$

If we choose an arbitrary condition such as $\lambda_i^{2/3}=1$, molecular volume $(V_m)=M \times K = p\lambda_i$ (lambdachor). *Lambdachor* ($p\lambda_i$) is thus a nice method of comparing molecular volumes of liquid substances when their internal latent heats of vaporisation are equal. The *lambdachors* ($p\lambda_i$) where obtained for different types of organic compounds—aliphatic, aromatic, and hydroaromatic hydrocarbons, esters, ketones, aldehydes, nitriles, and amines. From the molecular lambdachors, atomic lambdachors for atoms like carbon, hydrogen, oxygen, and nitrogen were calculated. It is generally additive in character, but constitutive effects are also obtained. The values for oxygen are different according as it is in the form of an ether, a ketone, or a carboxylate ester. Double and triple bonds also raise the values. Exaltation is also observed for six-membered rings like benzene, pyridine, naphthalene, or cyclohexane. The values for atomic lambdachors and other constitutive effects are shown in Table IV.

TABLE IV

Values of atomic lambdachors

Carbon	22.0	Oxygen (ester)	578.0
Hydrogen	162.0	Double bond	231.0
Nitrogen	110.0	Triple bond	461.0
Oxygen (ether)	203.0	Six-membered ring	74.0
Oxygen (ketonic)	410.0		

The experimental and calculated values of $\rho\lambda_i$ agree within experimental error and are shown in Table V for nearly 62 organic compounds of various types. A typical calculation is given for three liquids.

Benzene: $K=24.02$. $M=78$. $\rho\lambda_i$ (obs.)$=1873$.

$\rho\lambda_i$ (calc.)$=6C\times 6H+$values of double bonds + value of six-membered ring.

$=6+22+6\times 162+3\times 231+74=1871$.

Ethyl butyrate ($C_6H_{12}O_2$) : . $\rho\lambda_i$ (obs.)$=2645$.

$\rho\lambda_i$ (calc.)$=6\times 22+12\times 162+578=2654$.

Benzonitrile (C_7H_5N) : $\rho\lambda_i$ (obs.) $=2304$.

$\rho\lambda_i$ (calc.)$=7\times 22+5\times 162+110+3\times 231+461+74$, *i.e.*

$7C+5H+N+3$ double bonds + triple bond + six-membered ring$=2302$.

TABLE V

No.	Substance.	Formula.	$\rho\lambda_i$ Obs.	$\rho\lambda_i$ Calc.	%Diff.	Reference.
		A. Hydrocarbons				
1	Isopentane	C_5H_{12}	2083	2054	1.4	Young[25]
2	Pentane^n	C_5H_{12}	2132	2054	3.8	,,
3	Hexane^n	C_6H_{14}	2421	2400	0.9	,,
4	Heptane^n	C_7H_{16}	2753	2746	0.3	,,
5	Octane^n	C_8H_{18}	3095	3092	0.1	,,
6	Decane^n	$C_{10}H_{22}$	3805	3784	0.6	Luginin[20]
7	Dipropyl^i	C_6H_{14}	2401	2400	0.1	Young[25]
8	Dibutyl^i	C_8H_{18}	3106	3092	0.5	,,
9	Amylene	C_5H_{10}	1963	1961	0.1	Berthelot[17] Schiff[24]
10	Hexylene	C_6H_{12}	2311	2307	0.2	Young[25]
11	Cyclohexane	C_6H_{12}	2150	2150	0.0	,,
12	Methyl cyclohexane	C_7H_{14}	2496	2496	0.0	Kahlenburg[19], Luginin[20]
13	Benzene	C_6H_6	1873	1871	0.1	Young[25]
14	Ethyl benzene	C_8H_{10}	2578	2563	0.6	Schiff[24]
15	Propyl^n benzene	C_9H_{12}	2896	2909	0.5	,,
16	Toluene	C_7H_8	2224	2217	0.3	Kahlenburg[19]
17	Mesitylene	C_9H_{12}	2902	2909	0.3	Schiff Brown?
18	*o*-Xylene	C_8H_{10}	2558	2563	0.2	Brown[18]
19	*m*-Xylene	C_8H_{10}	2552	2563	0.4	,,
20	*p*-Xylene	C_8H_{10}	2564	2563	0.0	,,
21	Naphthalene	$C_{10}H_8$	2802	2819	0.6	Luginin[20],

TABLE V (contd.)

B. Esters.

No.	Substance.	Formula.	$\rho\lambda i$ Obs.	$\rho\lambda i$ Calc.	%Diff.	Reference.
22	Ethyl formate	$C_3H_6O_2$	1678	1651	1.5	Young
23	Ethyl acetate	$C_4H_8O_2$	1989	1962	1.4	Young
24	Propyl acetate	$C_5H_{10}O_2$	2314	2308	0.3	Brown
25	Butyl acetate	$C_6H_{12}O_2$	2690	2654	1.4	,,
26	Isobutyl acetate	$C_6H_{12}O_2$	2682	2654	1.0	,,
27	Isoamyl acetate	$C_7H_{14}O_2$	2987	3000	0.4	,,
28	Methyl propionate	$C_4H_8O_2$	1935	1962	1.4	Young
29	Ethyl propionate	$C_5H_{10}O_2$	2295	2308	0.6	,,
30	Isoamyl propionate	$C_8H_{16}O_2$	3335	3346	0.3	Brown
31	Isoamyl formate	$C_6H_{12}O_2$	2635	2654	0.7	,,
32	Ethyl butyrate	$C_6H_{12}O_2$	2645	2654	0.3	,,
33	Ethyl isobutyrate	$C_6H_{12}O_2$	2642	2654	0.5	,,
34	Isoamyl butyrate	$C_9H_{18}O_2$	3678	3692	0.4	,,
35	Ethyl valerate	$C_7H_{14}O_2$	3001	3000	0.0	Schiff
36	Ethyl isoval rate	$C_7H_{14}O_2$	2988	3000	0.4	,,
		C. Ethers.				
37	Diethyl ether	$C_4H_{10}O$	1922	1921	0.6	Young
38	Diethyl acetal	$C_6H_{14}O_2$	2763	2806	1.5	Luginin
39	Ethyl propyl ether	$C_5H_{12}O$	2259	2257	0.1	Nagornow[22] & Rotinjanz
40	Ethyl isobutyl ether	$C_6H_{14}O$	2610	2603	0.3	,,
41	Anisole	C_7H_8O	2385	2420	1.5	Luginin
		D. Nitriles.				
42	Acetonitrile	CH_3CN	1089	1101	1.1	Kahlenburg
43	Propionitrile	C_2H_5CN	1442	1447	0.3	Luginin
44	Butyronitrile	C_3H_7CN	1795	1793	0.1	,,
45	Capronitrile	$C_5H_{11}CN$	2501	2485	0.6	,,
46	Benzonitrile	C_6H_5CN	2304	2302	0.1	,,
		E. Aldehydes and ketones.				
47	Acetone	C_3H_6O	1449	1448	0.1	Young
48	Diethyl ketone	$C_5H_{10}O$	2133	2140	0.3	Luginin
49	Methylpropyl ketone	$C_5H_{10}O$	2138	2140	0.1	,,
50	Methyli sopropyl ketone	$C_5H_{10}O$	2127	2140	0.6	,,
51	Methylbutyl ketone	$C_6H_{12}O$	2478	2486	0.3	,,
52	Dipropyl ketone	$C_7H_{14}O$	2820	2832	0.4	,,
53	Methylhexyl ketone	$C_8H_{16}O$	3186	3178	0.3	,,
54	Acetophenone	C_8H_8O	2635	2649	0.5	,,
55	Benzaldehyde	C_7H_6O	2307	2303	0.2	,,

TABLE V (contd.)

F. Amines.

No.	Substance.	Formula.	Obs.	Calc.	% Diff.	Reference.
56	Diethylamine	$C_4H_{11}N$	1978	1980	0.1	Nadejdin[21]
57	Amylamine	$C_5H_{13}N$	2327	2326	0.0	Kahlenburg
58	Aniline	C_6H_7N	2122	2143	1.0	Luginin
59	Methylaniline	C_7H_9N	2467	2489	0.9	,,
60	Dimethylaniline	$C_8H_{11}N$	2816	2835	0.7	,,
61	Pyridine	C_5H_5N	1793	1798	0.3	Kahlenburg
62	Piperidine	$C_5H_{11}N$	2085	2076	0.4	Luginin

If lambdachor ($\rho\lambda_i$) is a true measure of the molecular volume, there should be an intimate relationship between this constant and critical volume (V_c). Table VI shows that this ratio is approximately 6.88, though it varies slightly from substance to substance. The last column gives the ratio of Sugden's[26] parachor (P) to the critical volume.

TABLE VI

Substance.	$\rho\lambda_i$.	V_c.	$\rho\lambda_i$.	P/V_c.
Benzene	1872.0	256.1	7.31	0.81
Diethyl ether	1922.0	281.9	6.87	0.75
Ethyl acetate	1988.3	286.0	6.95	0.76
Iso pentane	2083.0	307.2	6.78	0.76
Pentane[n]	2132.0	309.8	6.88	0.75
Propyl acetate	2314.0	344.9	6.71	0.75
Ethyl propionate	2295.0	343.9	6.81	0.74
		Mean	6.88	0.77

Thus it is observed that *lambdachor* ($\rho\lambda_i$) is nearly nine times Sugden's *parachor* ($\rho\lambda_i = 9P$) for non-associated liquids. For associated liquids it is high (16-23). Mean collision areas (a) of molecules of four different substances are compared with those of Sugden's[26] parachor and lambdachor in Table VII. The ratio in the last column is found to be roughly constant. Better agreement cannot be expected since many molecules are not symmetrical and $(\rho\lambda_i)^{2/3}$ is only a rough measure of the molecular cross-section.

TABLE VII

Substance.	a.	$(P)^{2/3}/a$	$(\rho\lambda_i)^{2/3}/a$
Benzene	13.83×10^{-16}	2.52×10^{-16}	10.98×10^{-16}
Ethyl acetate	15.01	2.41	10.47
Propyl acetate	15.11	2.30	10.22
Methane	7.72	2.27	9.92

There is an intimate relationship among lambdachor ($\rho\lambda_i$), critical temperature (T_c), critical volume (V_c), and boiling point (T_b). It is given by

$$\rho\lambda_i = \frac{9}{2} \times \frac{V_c T_c}{T_b}$$

The entropy of most of the unassociated liquids is approximately 20.78, though it varies from 20.5 to 21.05. For benzene and other hydrocarbons, this entropy change ($\triangle S$) is related to lambdachor, critical volume, critical temperature, and boiling point. Therefore, the above expression can be written as

$$\rho\lambda_i = \frac{\triangle S \times V_c \times T_c}{4.575 \times T_b} = \frac{\triangle S \times V_c T_c}{\sqrt{\triangle S} \times T_b} = \frac{\sqrt{\triangle S} \times V_c T_c}{T_b}.$$

Table VIII shows this relationship for some typical substances.

TABLE VIII

Substance.	V_c.	T_c.	$\rho\lambda_i$ (calc).	$\rho\lambda_i$ (obs).
Benzene	256.4	1.59	1838	1873
Pentane[n]	310.2	1.52	2173	2132
Ether	282.0	1.52	1929	1922
Ethyl acetate	286.3	1.55	1989	1989
Acetone	216.6	1.54	1501	1449
Cyclohexane	307.5	1.56	2158	2150

Eötvös[27] deduced the general equation, $\gamma[(M_v)]^{2/3} = K(t_c - t)^n$, from the assumption that bodies, which are in corresponding states, are also similar in mechanical respects of the forces between their corresponding parts, and their energies. He found that n was equal to one. This was modified by Ramsay and Shields[28], but the best modification was by Katayama[29] who gave it the form of

$$\gamma\left(\frac{M}{D-d}\right)^{2/3} = K(t_c - t)^n$$

where $K = 2.1$ and $n = 1$, for normal liquids. This has given us one of the good methods for determining the molecular weights of liquids from the knowledge of surface tension, density of liquid and vapour, and temperature. When we come to internal heat of vaporisation, which is a similar form of energy, a similar form of equation should hold good, or,

$$\lambda_i\left(\frac{M}{D-d}\right)^{2/3} = K(t_c - t)^n \text{ or } \lambda_i\left(\frac{M}{D-d}\right)^{2/3} = K(t_c - t)^{1/4}.$$

We found that when $n = 0.25$, the equation holds good for all normal liquids for temperatures ranging from zero to the critical temperature, as recorded in Table IX

TABLE IX

Values of log K at different temperatures.

Substance.	0°.	20°.	40°.	60°.	70°.	80°.	90°.	100°.	120°.	140°.
Benzene	2.6729	2.6761	2.6743	2.6751	2.6755	2.6777	2.6758	2.6727	2.6751	
CCl_4	2.3878				2.3869	2.3868		2.3849		2.3795
Pentane	2.7253		2.7172	2.7243		2.7214		2.7192	2.7259	2.7271

	0°.	140°.	160°.	180°.	200°.	220°.	240°.	260°.	270°.
Chlorobenzene	2.6254	2.6139	2.6169	2.6205	2.6203	2.6241	2.6283	2.6296	2.6293

In Table IX, the values of log K for a particular liquid are constant at different temperatures. This equation thus gives us a new method of determining the molecular weight of non-associable liquids. This method has been verified by us for a number of liquids. Just as Ferguson[30] deduced Mcleod's empirical relationship from Katayama's equation, it is possible to deduce the empirical relationship, $\lambda_i = K(D-d)^{3/2}$, by substituting the equivalent values of $(D-d)$ in place of (t_c-t) in Katayama's equation:

$$\lambda_i \times \left(\frac{M}{D-d}\right)^{2/3} = K\,(t_c-t)^{0.25}$$

But $$(t_c-t) = K(D-d)^{10/3}$$

$$\therefore \quad \lambda_i \left(\frac{M}{D-d}\right)^{2/3} = K.\,(D-d)^{10/3\times\frac{1}{4}} = K.(D-d)^{5/6}$$

$$\therefore \quad \lambda_i \times M^{2/3} = K\,(D-d)^{2/3+5/6}$$

$$\therefore \quad \lambda_i \times M^{2/3} = K(D-d)^{3/2}$$

Thus the fundamental empirical relationship, which is the basis of *lambdachor*, can be deduced from the Eötvös equation which has got the theoretical basis in the case of surface tension from the work of Madelung[31], Born[32], and Brillouin[33]. Surface tension and latent heat of vaporisation are different kinds of energy and what applies to surface tension can apply *mutatis mutandis* to latent heat of vaporisation.

Finally as lambdachor is more susceptible to constitutive influence than parachor, and as its value is much bigger than that of parachor, it is much easier to detect the constitutive factors in the molecule. Moreover, it gives a new method of comparing molecular volumes and of determining the molecular weight of non-associable liquids as well as the degree of association in the case of associable liquids. The values suggested for atomic lambdachors may require modification in the light of better and more accurate values of latent heat of vaporisation, but this does not affect the fundamental nature of the work and the new approach.

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Dezincification of Brasses

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Dezincification is the term applied to the preferential corrosion of zinc from copper-zinc alloys. It may be easily recognised by the copper-coloured appearance of the corroded metal. The selective corrosion of the base metal from the alloy is encountered in many cases, e.g., aluminium from aluminium bronzes or tin from tin bronzes. Dezincification of brass is the best example of the selective corrosion and it has been studied extensively for many years. There is, however, still disagreement about the mechanism of dezincification. The theories centre round the two main views. According to one view copper produced is residual, whereas the other view encompasses that copper is of the redeposited type. In the former, it is supposed that zinc is preferentially dissolved leaving copper behind. In the latter, it is assumed that initially both copper and zinc are dissolved, followed by redeposition of copper.

The earliest observation is that of Calvert and Johnson[1], who showed that an alloy of equal proportions of copper and zinc, immersed in concentrated hydrochloric acid, gave up in a few days the whole of zinc, leaving behind copper in spongy state. Tilden[2] considered the role of oxygen in the corrosion of brass and showed that no corrosion of brass took place if air were excluded.

Philip[3] believed in the existence of minute zinc-copper couples functioning as small electric cells all over the surface of the brass. Due to such couples the zinc is dissolved, leaving the copper behind.

Colegate[4] classified dezincification in two types: (a) plug type and (b) layer type, according as the dezincification penetrates perpendicularly or spreads horizontally on the specimen. The divison is arbitrary and merely indicates whether corrosion is localized or general.

Bengough and Hudson[5] consider that copper is not residual but is of 'redeposited' type. According to these authors, when brass is placed in chloride solution, the first attack affords a layer of copper oxide with a little zinc oxide, the zinc mainly going into solution as zinc chloride. The oxidised surface gradually changes into an almost insoluble cuprous chloride, which is ordinarily swept away by gravity or water currents, but which may adhere to the surface. If the insoluble chlorides adhere to the surface, cupric chloride is formed. Cupric chloride attacks zinc as well as copper, with formation of a soluble zinc chloride and deposition of a crystalline or powdery copper.

$$CuCl_2 + Cu \longrightarrow 2CuCl$$

$$CuCl_2 + Zn \longrightarrow ZnCl_2 + Cu$$

The transformation of brass to copper was once known as dezincification, but Bengough, Jones and Pirret[6] were the first to demonstrate clearly the redeposited part of copper. They termed this "apparent dezincification" to distinguish it from chemical dezincification of leaching out of the baser zinc metal.

Abrams[7] concluded that agitation favoured complete corrosion, whereas stagnation favoured dezincification. He further stated that maintenance of a film was necessary for dezincification. According to him dezincification may be obtained by artificial films, which would prevent removal of copper and cuprous salts.

The presence of a considerable amount of dissolved copper would also permit dezincification even in absence of a membrane. Bengough and May[8] confirmed Abrams' findings and further made a classical observation that small amounts of arsenic in brass could prevent dezincification.

Stillwell and Turnipseed[9] studied the corrosion of ϵ-brass and showed that powerful reagents like concentrated hydrochloric acid attacked both copper and zinc, copper being subsequently redeposited. On the other hand, weak reagents like dilute hydrochloric acid or acetic acid remove only the zinc atoms converting ϵ-brass first to γ-brass then to β-brass, and finally leaving residual copper. The weak reagents favour chemical dezincification, but strong reagents favour apparent dezincification.

Fink and Evans[10] state that in the initial stage of attack, the corrosion may consist of selective solution of zinc producing copper-rich areas, which may then promote electrochemical action. Evans[11] states that the effective reactions in either case are the same.

$$Zn \longrightarrow Zn + 2e \quad \text{(anodic reaction)}$$

$$O + H_2O + 2e \longrightarrow 2(OH^-) \quad \text{(cathodic reaction).}$$

According to him, thus the driving E.M. F. should be the same for both mechanisms, but in the first mechanism (residual copper theory) the resistance must soon become high since zinc ions have to thread their way through very fine pores in the copper. It is not easy to see how the first mechanism can persist after the first few atomic layers of brass have become dezincified. The first mechanism is important at the outset. The action usually starts at points abnormally rich in zinc, such as the grain boundaries where traces of β phase may be present even in 70/30 (α) brass[12]. Zinc-rich places will be anodic and both copper and zinc will dissolve. When copper compounds have sufficiently accumulated, metallic copper may be redeposited and the second mechanism can then continue.

There is considerable evidence in support of both the theories. Thus, Milton and Larke[13], Bassett[14], Polushkin[15], and Bialosky[16] consider that copper is residual, whereas Bengough and May[8], Hollomen and Wulff[17], Abrams[7], and Storey[18] are of the opinion that it is redeposited.

One of the factors influencing dezincification is the oxygen concentration of the solution. Low degree of aeration favours dezincification, whereas high degree of aeration brings about complete corrosion. High chloride ion concentration is also effective in inducing dezincification. Coupling of brass to a more cathodic metal may induce dezincification, but contact with anodic metal may prevent dezincification. Increase in the zinc content

of the alloy increases its susceptibility to dezincification. A mixture of α-and β-alloys is more susceptible than α-alloys. Arsenic and tin are good inhibitors of dezincification as these prevent deposition of copper. A practical remedy for dezincification exists for the α-brasses but not yet for the two-phase brasses. Arsenic appears to pass preferentially into the α phase leaving the more susceptible β phase unprotected. On the other hand, the addition of 1% tin to the two-phase brass reduces the rate of dezincification considerably. It is possible that the addition of tin or arsenic to brass so modifies the deposition potential of copper that deposition of initially dissolved copper is stopped. Retardation in dezincification may also be due to the fact that tin has a high hydrogen overpotential and that arsenic raises the hydrogen overpotential at a cathode.

Corrosion of various brasses such as α-brass (80/20, 70/30, 60/40) and $\alpha+\beta$-brass (59/41) has been studied by us in the presence of various acids and salts[19]. In an attempt to study the corrosion of brass we have tried to find out whether it is possible to distinguish clearly between the two types of dezincification and also to find out ways and means of reducing dezincification by modifying the medium. The dezincification is evident in the case of hydrochloric acid, phosphoric acid, and lactic acid. The action of these reagents alone may result in dezincification depending on the nature and concentration of the reagent and duration of the experiment. In some cases, such as malic, citric, and tartaric acids, there may initially be decuprification. This is due to complex formation between copper and anions of these acids.

The influence of H_2O_2 on corrosion by the acids afforded interesting results. In the case of α-brass, addition of H_2O_2 invariably results in reduction of dezincification to such an extent that there may even be cases of copper being preferentially dissolved. In presence of H_2O_2, deposited copper is redissolved or prevented from being redeposited. The addition of H_2O_2 favours complex formation between copper and anions of these acids. According to Evans' stagnant condition favours dezincification, whereas aeration favours dissolution of the alloy as a whole. Addition of H_2O_2 may be beneficial in pickling of α-brass as it would reduce dezincification. The behavour is quite different in the case of $\alpha+\beta$ brass. Addition of small amounts of H_2O_2 results in increase of dezincification. This is in accordance with the observation of Uhlig[20], that corrosion of zinc is accelerated in presence of oxygen. Even in $\alpha+\beta$-brass, further addition of H_2O_2 leads, however, to a decrease in dezincification. In presence of small amounts of H_2O_2, the attack on β phase is augmented; further addition of H_2O_2, however, results in attack of both the phases. Thus small amounts of H_2O_2 clearly distinguishes electrochemical and chemical dezincification, former being reduced and the latter being increased.

The study of the influence of inhibitors on the corrosion of α-(60/40) and $\alpha+\beta$-(59/41) brasses by NH_4Cl (1.0N—5 days) revealed the following results:

TABLE I

(Size of the specimen=6 cm×3 cm. Thickness=28. s.w.g.)

Reagent.	α-Brass (60.7% Cu-39.1%Zn)		$\alpha+\beta$-Brass (59/41).	
	Corrosion.	Ratio (Cu/Zn).	Corrosion.	Ratio (Cu/ Zn).
Blank (1.0N-NH_4Cl)	36.6 mg.	0.0139	41.7 mg.	0.0024
Agar (0.2%)	85% Reduction		87% Reduction	—
Dextrin (0.2%)	102% Increase	0.93	25% ,,	0.030
Acacia (0.2%)	175% ,,	0.98	47% ,,	0.023
Gelatine (0.2%)	252% ,,	0.80	12% Increase	0.80
Urea (0.2%)	295% ,,	1.48	3% ,,	0.0024

Agar reduces corrosion to nearly 1/6th the value in the case of both the brasses. Hence it may be employed as a general inhibitor. For α-brass gelatine, dextrine, acacia, or urea increases attack and reduces dezincification. In the case of $\alpha+\beta$-brass, urea has practically no influence on the mode and extent of corrosion, whereas the attack is retarded in the case of acacia and dextrin. The action of these reagents may serve to distinguish between chemical and electrochemical dezincification. Urea is the best example. It increases corrosion when dezincification is of the electrochemical type, but is without any influence on the mode and extent of corrosion where dezincification is of the leaching type. Gelatine is the only inhibitor which reduces dezincification of $\alpha+\beta$-brass.

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Oxidimetric Determination of Organic Derivatives of Hydrazine

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Hydrazine is a powerful reducing agent. Hydrazino group (>N-N<) in hydrazine and its derivatives is easily oxidised. Methods for the estimation of hydrazine and its derivatives are therefore based on quantitative oxidation of the hydrazino group by various oxidising agents under properly controlled conditions to avoid the occurrence of side reactions. Hydrazine on oxidation gives different end products, viz., nitrogen and ammonia, hydrogen azide and ammonia, or nitrogen only as oxidation products, depending on conditions of the reaction and type of oxidant used[1]. Hofman and Kuspert[2] described the use of ammonium metavanadate as an oxidant for volumetric and nitrometric determination of hydrazine. Jamieson[3] developed a visual method for the determination of hydrazine with potassium iodate in hydrochloric acid medium using chloroform as indicator. The organic layer, which was coloured pink due to iodine, became light pale yellow at the end point due to the formation of iodine monochloride. Roberto and Roncali[4] observed quantitative oxidation of hydrazine with permanganate.

Kolthoff[5] stated that best results were obtained when alkaline permanganate was used for the estimation of hydrazine. Chattaway[6] studied the reaction of metallic oxides, permanganates, and chromates with several primary aromatic hydrazines, which on oxidation formed unstable hydroxyhydrazine. In presence of an alkali, this unstable compound immediately decomposed to a hydrocarbon, nitrogen, and water.

$$RNH.NH \longrightarrow RNH.NHOH \longrightarrow RH + N_2 + H_2O$$

Browne and Shetterly[7] studied the action of potassium persulphate, potassium permanganate, hydrogen peroxide, red lead, manganese dioxide, potassium perchlorate, sodium periodate, lead dioxide, potassium chlorate, potassium bromate, and potassium iodate in acid solution on hydrazine, and found that in most cases nitrogen and ammonia were the oxidation products. Datta and Choudhry[8] studied the action of halogens and their oxyacid salts on semicarbazide hydrochloride, semioxamide and oxalylhydrazine in hydrochloric and sulphuric acid media. They estimated the

hydrazine derivatives by measuring the volume of nitrogen evolved during the reaction[8]. Ling and Nanji[9] used iodine as an oxidising agent for the estimation of phenylhydrazine. Kurtenacker and Wagner[10] estimated hydrazine in a mixture of hydroxylamine and hydrazine by oxidising the mixture with excess potassium bromate solution in presence of hydrochloric acid. Hydrazine present in the mixture was calculated from the volume of nitrogen gas evolved.

Gilbert[11] titrated hydrazine electrometrically with iodine in disodium phosphate buffer solution instead of sodium bicarbonate or sodium potassium tartrate, as recommended by earlier investigators. Kurtenacker and Kubina[12] described volumetric estimation of hydrazine and some of its derivatives with a standard solution of bromate and iodate in acid medium using indigo and chloroform as indicators respectively. Lang[13] used potassium iodate in acid solution for the determination of hydrazine by adding potassium cyanide to the reaction mixture:

$$IO_3^- + N_2H_4 + HCN + H^+ = N_2 + ICN + 3H_2O$$

and titrating the iodine cyanide formed with sodium thiosulphate.

Hovorka[14] proposed a new method for the determination of hydrazine and semicarbazide by oxidising them with excess potassium iodate in presence of mercuric perchlorate, which prevented liberation of iodine due to binding of iodide formed during the reaction. Komarowsky *et al.*[15] have recommended the use of chloramine-T for direct volumetric estimation of hydrazine in presence of sodium bicarbonate and potassium iodide using starch as an indicator. Miller and Furman[16] titrated phenylhydrazine and semicarbazide with potassium iodate in hydrochloric acid solution in presence of mercuric chloride to a potentiometric end point. Singh and Rehman[17] used chloramine-T for potentiometric determination of hydrazine in acid solution. Szebelledy and Madis[18] titrated hydrazine with potassium bromate in presence of phosphoric acid at 60-80°, using phosphomolybdic acid as redox indicator. Dernbach and Mehlig[19] oxidised hydrazine sulphate with alkaline potassium ferricyanide; ferrocyanide formed was titrated with ceric sulphate in sulphuric acid medium. Vulterin and Zyka[20] determined hydrazine by direct potentiometric titration with potassium ferricyanide in alkaline medium.

McBride *et al.*[21] carried out potentiometric titrations of a number of organic derivatives of hydrazine with potassium iodate in both hydrochloric and sulphuric acid media. They showed that each hydrazino group in monosubstituted hydrazines, their hydrazones, and acyl derivatives is oxidised with a four-electron change:

$$N_2H_5^+ \longrightarrow N_2 + 5H^+ + 4e^-$$

Singh *et al.*[22] used potassium metaperiodate and chloramine-B in hydrochloric acid medium for potentiometric determination of hydrazine. They also used potassium metaperiodate as an oxidising agent for volumetric estimation of hydrazine sulphate and phenylhydrazine. Gottlieb[23] determined hydrazine with sodium hypobromite using the gasometric technique. Chalik *et al.*[24] used iodine monochloride in neutral or slightly acidic solution for potentiometric determination of thiosemicarbazide. They also used iodine monochloride for visual and potentiometric titrations in the estimation of hydrazine and phenyl-

hydrazine in sodium bicarbonate buffer. Issa and Issa[25] determined hydrazine indirectly by oxidising it with an excess of potassium permanganate in alkaline solution in pressence of telluric acid. They carried out potentiometric titrations of hydrazine with potassium permanganate in presence of barium ions at varying concentrations of sodium hydroxide.

Litvineko *et al.*[26] carried out potentiometric titrations of carboxylic acid hydrazines and their hydrazones with sodium nitrite. Vulterin and Zyka[27] used sodium nitrite as volumetric reagent for the potentiometric determinations of hydrazine sulphate, semicarbazide hydrochloride, thiosemicarbazide, and phenylhydrazine hydrochloride in different acid media. Singh *et al.* have used chloramine-B[28], chloramine-T[29], potassium metaperiodate[30], sodium metavanadate[31], diethylenetetra-ammonium sulphatocerate[32], and sodium hypochlorite[33] as oxidants for determination of hydrazine in presence of hydrochloric acid using iodine monochloride-chloroform as indicator in visual titrations. McKennis *et al.*[34] carried out gasometric determination of hydrazine and its derivatives by using potassium iodate as an oxidant. Paul and Singh[35] have used potassium chlorite as volumetric reagent for the estimation of hydrazine sulphate. Schulek and Burger[36] employed bromine chloride for volumetric titrations of hydrazine and its derivatives using *p*-ethoxychrysodine as an indicator.

Suseela[37] has estimated hydrazine by titrating it potentiometrically with alkaline potassium ferricyanide in presence of osmium tetroxide. Sant and Mukherji[38] have carried out amperometric titrations of hydrazine sulphate with potassium bromate using rotating platinum electrode. Berka and Zyka[39] have stated that in solution buffered with sodium bicarbonate, borate or sodium acetate, potassium metaperiodate can be titrated potentiometrically with hydrazine sulphate. Singh and Kashyap[40] have used iodine trichloride as a volumetric reagent for the determination of hydrazine sulphate in acid medium.

In this study some organic derivatives of hydrazine have been determined by a volumetric method using sodium vanadate[41], chloramine-T[42], potassium periodate[43], potassium bromate[44], sodium hypochlorite[45] and diethylenetetra-ammonium sulphatocerate[46] as oxidants.

Methods for the estimation of hydrazine and its derivatives are based on quantitative oxidation of hydrazino group present in each of the compounds. Although the hydrazino group is readily oxidised yet its quantitative oxidation is only effected under properly controlled conditions.

Oxidation of hydrazine has been a subject of critical study for the past fifty years or so. During this period several theories have been proposed by various investigators to explain the oxidation mechanism of hydrazine.

Browne *et al.*[7] made a detailed study of the action of various oxidising agents on hydrazine in acid medium and formulated an oxidation mechanism to account for the formation of different oxidation products of hydrazine when different oxidants were used under similar conditions. Oxidising agents such as ferric, manganic, nickelic, cobaltic, cupric, and ceric ions oxidise hydrazine to nitrogen or to nitrogen and ammonia with one-electron change through the intermediate formation of tetrazane ($H_2N.NH.NH.NH_2$).

$$N_2H_4 \longrightarrow (N_2H_3)+H^+ + e^-$$

$$2(N_2H_3) \longrightarrow (H_2N.NH.NH.NH_2) \longrightarrow N_2+2NH_3$$

Oxidising agents such as persulphate, peroxide, chlorate, bromate, and molybdate ions oxidise hydrazine with two-electron change to hydrogen azide and ammonia through the intermediate formation of tetrazene ($H_2N.N{=}N.NH_2$).

$$N_2H_4 \longrightarrow (N_2H_2)+2\overset{+}{H}+2e^-$$

$$2(N_2H_2) \longrightarrow (H_2N.N{=}N.NH_2) \longrightarrow HN_3+NH_3$$

Permanganate, dichromate and iodate oxidise hydrazine to nitrogen with a four-electron change.

$$N_2H_4 \longrightarrow N_2+4\overset{+}{H}+4e^-$$

Abel[47] studied the action of permanganate and maganic ions on hydrazine and has put forward its oxidation mechanism with these oxidants. He assumed that hydrazine plays a dual role. It can either act as an electron donor ($N_2H_4 \rightarrow NH_2+NH^+_2+e^-$) or act as an electron acceptor ($N_2H_4+e^- \rightarrow NH_2^-+NH_2$). When it acts as an electron donor it is oxidised to nitrogen and when it acts as an electron acceptor, it is reduced to ammonia.

Higginson *et al.*[48] have discussed the classification of oxidising agents as two- or one-electron transfer reagents, depending on the products of their reaction with hydrazine. They stated that quantitative oxidation of hydrazine to nitrogen by two-electron transfer oxidants is in accord with the scheme in which N_2H_2, once formed, can lead to nitrogen and not to ammonia. They explained the variable stoichiometry obtained

$$N_2H_4 \xrightarrow{-2e^-} N_2H_2 \xrightarrow{-2e^-} N_2$$

with one-electron transfer reagents due to two competing reactions which follow the initial formation of N_2H_3.

$$N_2H_4 \xrightarrow{-e^-} N_2H_3$$

$$2N_2H_3 \xrightarrow{\text{dimerisation}} N_4H_6 \longrightarrow N_2+2NH_3 \qquad .. \qquad .. \qquad (a)$$

$$N_2H_4 \xrightarrow{-e^-} N_2H_2 \xrightarrow{-2e^-} N_2 \qquad .. \qquad .. \qquad .. \qquad (b)$$

Reaction (*a*) leads to a stoichiometry of 1 and (*b*) to stoichiometry of 4; so the stoichiometry for one-electron transfer reagents may lie between 1 and 4 depending on the proportion of these two reactions. They further stated that in alkaline medium one-electron transfer reagents produce only nitrogen quantitatively on oxidation of hydrazine by a four-electron change.

Higginson and Sutton[49] have also studied the mechanism of oxidation of hydrazine using ^{15}N isotope as a tracer element. They showed that no N–N bond fission occurred and no new N–N bonds were formed when hydrazine was quantitatively oxidised to nitrogen.

$$N_2H_4 \xrightarrow{-4e^-} N_2$$

McBride *et al.*[21] have shown that nature and proportions of the end-products of the oxidation of hydrazine and its derivatives vary with the specific nature and the oxidation-reduction potential of the oxidising system, and with the *p*H of the medium.

Powell and Cahn[50], Higginson and Wright[51], and Roseinsky[52] have studied kinetics of the oxidation of hydrazine with ferric iron and proposed the following oxidation mechanism to account for the formation of nitrogen and ammonia as oxidation products.

$$Fe(III)+N_2H_4 \rightarrow Fe(II)+N_2H_3+H^+$$

$$Fe(II)+N_2H_3+H^+ \rightarrow Fe(III)+N_2H_4 \text{ (backward reaction)}$$

$$2N_2H_3 \xrightarrow{\text{dimerisation}} N_4H_6$$

$$N_4H_6 \xrightarrow{\text{fast}} N_2+2NH_3 \quad \ldots \quad \ldots \quad (1)$$

$$2N_2H_3 \rightarrow N_2H_4+N_2H_2$$

$$2Fe(III)+N_2H_2 \xrightarrow{\text{fast}} 2Fe(II)+N_2+2H^+ \quad \ldots \quad \ldots \quad (2)$$

$$Fe(III)+N_2H_3 \rightarrow N_2H_4+Fe(II)+H^+$$

$$2Fe(III)+N_2H_2 \xrightarrow{\text{fast}} 2Fe(II)+N_2+2H^+ \quad \ldots \quad \ldots \quad (3)$$

In reaction (1) hydrazine is oxidised with one-electron change to nitrogen and ammonia and in reactions (2) and (3), oxidation of hydrazine to nitrogen takes place with a four-electron change. This is in agreement with the findings of Abel[47] and Higginson *et al*[48].

Kolthoff *et al.*[53] have studied the mechanism of oxidation of hydrazine with ferric ethylenediamine tetra-acetate (FeY^-) in borax and phosphate buffers with and without *ortho*-phenanthroline. They found that the oxidation product of hydrazine is mainly nitrogen. A very small amount of ammonia was formed in accord with the reaction ratio of 3.7 to 4.0 moles of FeY^- consumed per mole of hydrazine. They suggested the reaction mechanism, which is similar to that given by Powell and Cahn[50], Higginson and Wright[51], and Roseinsky[52], where N_2H_3 is supposed to be formed giving rise to nitrogen or to nitrogen and ammonia when hydrazine is oxidised.

In the investigations carried out by the present authors sodium vanadate, chloramine-T, potassium iodate, potassium bromate, sodium hypochlorite, and diethylenetetraammonium sulphatocerate were used to determine hydrazine and some of its organic derivatives in acid medium by an extraction end-point method or a potentiometric method. In case of potassium bromate, *p*-ethoxychrysodine was also used as an indicator. In case of potassium periodate a large amount of iodine was liberated during the titration, done

very carefully in presence of a large amount of hydrochloric acid to avoid the loss of the liberated iodine. In titrations with the other oxidants, a few c.c. of iodine monochloride were used as a catalyst and indicator. An advantage of using iodine monochloride over the conventional procedure in iodate and periodate titrations is that it does not involve liberation of large quantities of iodine with the subsequent risk of loss.

Although chloramine-T and sodium hypochlorite oxidised hydrazine and its derivatives instantaneously at low hydrochloric acid concentrations (2.0*N* to 5.0*N* and 2.0*N* to 2.5*N* in case of chloramine-T and sodium hypochlorite respectively), yet these reagents are not very suitable due to deterioration with time. These are to be prepared afresh and standardised when required for use. The titrations with diethylenetetra-ammonium sulphatocerate and sodium vanadate are done in hydrochloric acid medium of normality varying from 6.0*N* to 7.5*N*. Potassium bromate oxidises the organic derivatives of hydrazine at a faster rate than the sulphatocerate or sodium vanadate. Normality of hydrochloric acid is to be kept between 4.0*N* and 6.0*N* during the titration with potassium bromate when iodine monochloride is used as a catalyst and indicator. Moreover, potassium bromate is a primary standard in volumetric analysis.

It is found that the hydrazine derivative containing electrophilic groups, such as >CO or $-NO_2$, retard the rate of oxidation by any of the oxidants used in this investigation. This effect is so dominating in case of dibenzoylhydrazine ($C_5H_5CO.NH.NH.COC_6H_5$) that it is rather difficult to oxidise it quantitatively. Although phenyl ($-C_6H_5$) group normally acts as an electron attracting group, yet it produces a positive inductomeric effect, *i.e.*, on demand by a reaction centre it can supply electrons. Hydrazine derivatives containing phenyl group are therefore very easily oxidised.

On the basis of the experimental results it can be stated that the organic derivatives of hydrazine are oxidised by a four-electron change per hydrazino group to nitrogen with the oxidants used in this investigation.

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Diterpenoids

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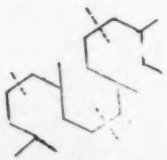
Investigations during the last forty years on the basis of the "Isoprene rule" have resulted in the elucidation of the structure, stereochemistry, and in many cases the absolute configuration of a large number of terpenoids due, no doubt to the development of infrared and nuclear magnetic resonance spectroscopy, spectropolarimetry, mass spectrography, and vapour phase chromatography. These powerful physical tools have recently revealed many a finer aspect of the molecular patterns hitherto unsuspected in related fields.

It is proposed to restrict this review to recent advances in diterpenoids excluding, however, the diterpenoid alkaloids[1]. Diterpenoids can be classified as being built up of four C_5 units representing a wide class of naturally occurring compounds, such as acids, alcohols, lactones, ethers, and furanoids, besides hydrocarbons. One of the most intensively studied members of this group is abietic acid, the molecular framework of which was clearly established in 1941; but this could not be fitted into the isoprene rule. A few isomers were then known and in some, a different carbon skeleton had also been established at that time. Until recently the entire field was considered to be extremely complicated because of inadequate understanding of the rearrangements that were generally associated with these types of molecules. More recently, a large variety of diterpenoids have been isolated not only from the plant kingdom but also from mould metabolites. It has now become possible to systematise hitherto-unrelated compounds from a well-ordered C_{20}-chain on experimentally documented reaction mechanisms. A close inspection of these types suggests common mechanistic features in spite of apparent diversity. The most cardinal one in the entire mechanistic spectrum is the migration of quaternary methyl groups to adjacent positions in carbocyclic systems. On this basis, these may broadly be classified, as shown below, taking into account some representative members of each category.

Classification

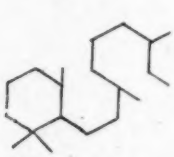
(1) *Open-chain:*



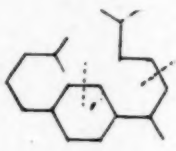
Phytol

(I)

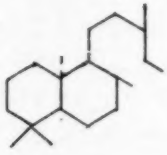
(2) *Carbocyclic rings:* (*i*) *Monocyclic* (II and III); (*ii*) *Bicyclic* (IV) sclareol, manoöl, aganthene-dicarboxylic acid, marrubiin, eperuic acid, labdanolic acid, cativic acid, and ketolabdanolic acid[3].



Axerophthol or Vitamin A
(II)



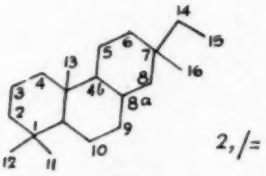
Camphorene[2]
(III)



(IV)

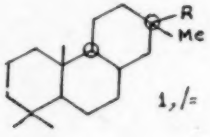
The carbon framework of columbin[4] originates from migration of two quaternary methyl groups at C_1- and C_{4a}- to adjacent positions, C_{10a}- and C_{4b}- respectively (cf. *iii* (f) *vide infra* and Friedelin[5]).

(iii) Tricyclic



(VI)

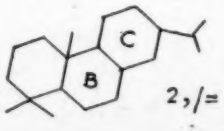
(*a*) *Pimanthrene series*, i.e., affording pimanthrene on dehydrogenation.



(VII: R= vinyl, $\Delta^{8(8a)}$)
(VIII: R= $-CHOH.CH_2OH$, $\Delta^{8a(9)}$)

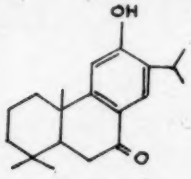
Pimaric acid (dextro[6]-pimaric acid), 4b- α(H), 7-β(vinyl). Isopimaric acid (isodextro[6]-pimaric acid), 4b-β(H), 7- α(vinyl).[7] Sandaracopimaric acid (C_7-epimer of pimaric acid)[8]. Cryptopimaric acid (formerly considered to be C_{4b}-epimer[9a] of pimaric acid)[9b].

Migration of methyl ($C_7 \rightarrow C_{14}$) evidently through carbonium ion mechanism, subsequently realised experimentally by Wenkert[10].

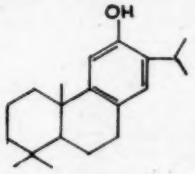


(IX)

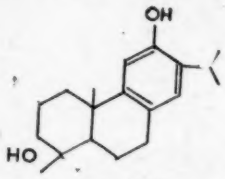
(*b*) ***Retene series,*** **i. e., affording retene or its derivatives on dehydrogenation.**



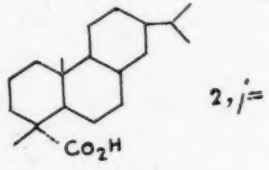
Sugiol
(X)



Ferruginol
(XI)



Hinokiol
(XII)



(XIII)

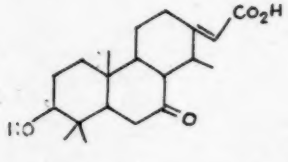
Abietic acid[7], $\Delta^{7(8),\ 8a(9)}$

Neoabietic acid[7], $\Delta^{7(14),\ 8(8a)}$

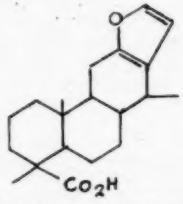
Palustic acid[7], $\Delta^{4b(8a),\ 7(8)}$

Teloabietic acid[7,12], $\Delta^{7(8),\ 14(15)}$

(*c*) ***Migration of methyl*** ($C_7 \rightarrow C_8$) **inside the ring.**



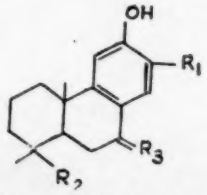
Cassaic acid
(XIV)



Vinhaticoic acid, vouacapenic acid
(XV)

Vinhaticoic and vouacapenic acids are epimeric at C_4.

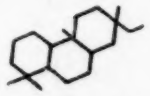
(*d*) ***Loss of isopropyl group.***



Podocarpic acid ($R_2=\beta$-CO_2H, $R_1=H$, $R_3=H_2$)
(XVI)

(*e*) *Loss of* C_7*-ethyl group*. Nimbiol (R_2=R_1=Me, R_3=O in XVI).

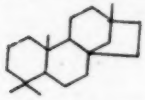
(*f*) *Migration* of C_{4a}-methyl group (cf. γ-lactone from dihydropimaric acid)[10].



Rosenolactones[13]

(XVII)

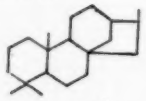
(*iv*) *Tetracyclic*



Mirene

(XVIII)

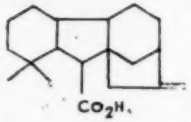
(*b*) *Migration of* c_7*-methyl group.*



Phyllocladene, steviol

(XIX)

(*c*) *Loss of* C_{4a}- *methyl group* and subsequent contraction of the ring.

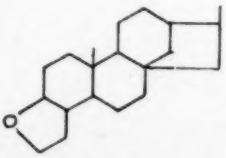


Gibberellins[14]

(XX)

CO_2H group originates from C_9– and this has been established through tracer technique[15].

(*d*) *Migration of methyl* ($C_1 \rightarrow C_{11}$; cf. methylabietin[16]) to form the ethyl chain. This accounts for the skeleton of cafestol and kahwiol and the ethyl chain forms a furan ring involving the oxygenated C_2- position.



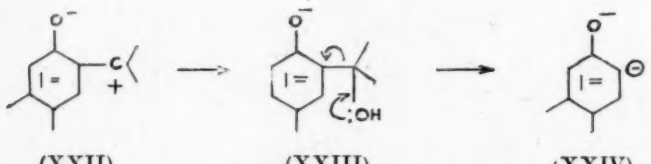
(XXI)

Resin acids can again be classified into two fundamental groups depending on stereochemistry of C_4-carboxyl with respect to C_{4a}- methyl group. In abietic acid and pimaric acid, it is α- and in podocarpic acid and aganthene dicarboxylic acid, it is β-. Biogenetically this may be of great taxonomical interest, but from synthetic studies (*vide infra*) this is also quite significant. Chemically, it has been possible to develop diagnostic methods to differentiate the stereochemistry of the carboxyl groups. The classical method of alkaline hydrolysis[17] has so long been utilised to differentiate this system, as the β-oriented ester group is very difficult to hydrolyse except under drastic experimental conditions. Recently two other methods have also been found applicable for this purpose. One is due to Wenkert and Jackson[18]. The β-oriented ester group is converted into the carboxyl with lithium and liquid ammonia and the α-oriented ester group is reduced to the primary alcohol. Another ingenious method[19] through determination of the apparent dissociation constants of the isomeric acids has been successfully developed by Prof. Prelog in Zürich. The pK value of the β-oriented carboxyl group is (8.4-8.5) and that of α-oriented carboxyl group is (8.0-8.1).

Biogenesis

In 1956, Cocker *et al.*[20] proposed a hypothesis that the biogenesis of di- and tri-terpenoids is based on different mechanisms. Cyclisation of polyene chain for the formation of diterpenoids was supposed to proceed through participation of protons. Their main arguments were the non-occurrence of di- and tri-terpenoids together in plants and also diterpenoids having no hydroxyl function at C_2. Isolation[21] of nimbin and nimbiol from *Malia azadirachta*, Linn. is a unique observation. Another significant factor that has emerged during these studies is that in recently isolated C_2-hydroxyditerpenoids and in eperuic acid, C_{4a}-methyl has an absolute configuration opposite to that present in C_2- non-oxygenated diterpenoids, triterpenoids and steroids. A new comprehensive biogenetic scheme has got to be evolved which can offer a unifying concept emphasising the common origin of terpenoids and steroids. In this connection, it is worth mentioning that molecular oxygen[22], and not the OH^+ originally proposed by Ruzicka, is the effective initiator in the cyclisation of polyenes for the biosynthesis of polyisoprenoids.

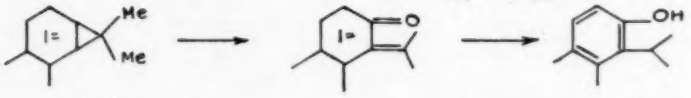
Coming to the more specific examples, it is to be noted that ring C is attended with aromatisation at some stage of the phytochemical oxidation with concomitant introduction of hydroxyl at C_6-. In this connection the presence of hinokiol is quite significant. It may be interesting to suggest the following pathway for the loss of isopropyl group leading to podocarpic acid.



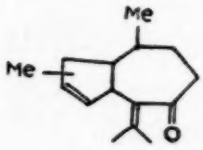
(XXII) (XXIII) (XXIV)

This is quite analogous to that suggested for the biogenesis of furan derivatives[23]. This again brings in line with the mechanism put forward by Sen Gupta *et al.*[21] for the loss of ethyl group resulting in nimbiol. This circumvents the role of steric factors inherent in the mechanism proposed by Wenkert[24]. It fails to explain, however, the migration of isopropyl

group leading to the structure of totarol, whereas the mechanism suggested by Wenkert appears to be quite novel. It may be worthwhile to suggest that the migration of isopropyl takes place through the formation of a cyclopropane derivative followed by oxidative fission. A close analogy may be found in the partial structure of zierone[25] (XXVIII)

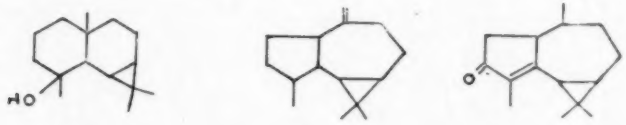


(XXV) (XXVI) (XXVII)



(XXVIII)

where the isopropyl group has migrated to the neighbouring position evidently through a cyclopropane intermediate. Recently, quite a few analogous compounds, maaliol (XXIX), aromadendrene (XXX), and cycloclorenone (XXXI), have been isolated and the fission of the cyclopropane ring in the desired direction has also been achieved.



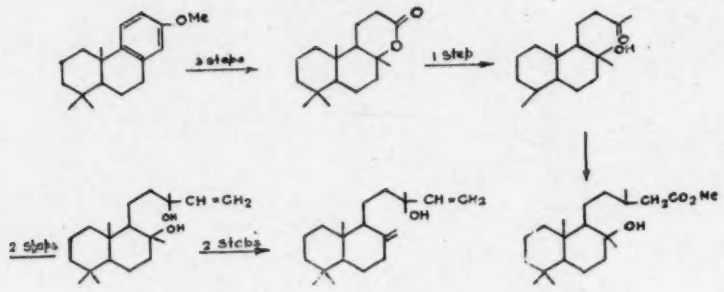
(XXIX) (XXX) (XXXI)

It may be emphasised here that no diterpenoid with a cyclopropane ring has so far been isolated from natural sources although triterpenoids containing cyclopropane ring are already known, *e.g.*, cycloartenol, cyclolandenol and phyllanthol[26].

Synthesis

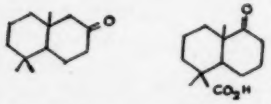
Synthetic studies in this field were far behind. Fruitful attempts in this direction have been initiated during the last few years. The apparent difficulty in the past had been the devising of suitable stereoselective methods with a view to avoiding the stereochemical complexities arising from lack of proper knowledge of their structures and stereochemistry. The earliest success in this field may be said to be the synthesis of phytol by Karrer[27]. Attempts towards synthesis of the monocyclic derivatives, particularly vitamin-A, have been quite extensive, resulting in its total synthesis by Isler[28]. In the bicyclic system, successful approaches have been made by Lederer[29] and particularly by Bartlop[30] for the synthesis of sclareol (XXXVI), methyl labdanolate (XXXV), its C_{13}-isomer, and (C_{13}-iso)-manoöl (XXXVII). Recently sclareol has been converted[31] to manoöl.

(XXXII) (XXXIII) (XXXIV)



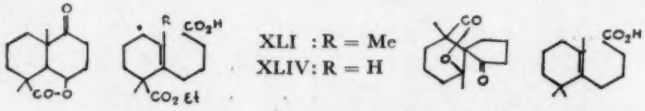
(XXXVI) (XXXVII) (XXXV)

A comprehensive series of experiments on the synthesis of terpenoids has been initiated in this laboratory since 1952 and some of the results achieved so far have been published[32]. Synthesis of the bicyclic ketone (XXXVIII) (semicarbazone, m.p. 221-22°) and of the keto-acid (XXXIX, m.p. 161°) of known stereochemistry have been accomplished (G. Banerjee, unpublished work) and these may be looked upon as important building units towards the synthesis of bicyclic diterpenoids.



(XXXVIII) (XXXIX)

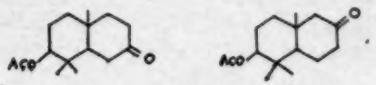
With a view to synthesising marrubiin, attempts were made (S. L. Mukherjee, D.Phil. Thesis, Calcutta University, 1959) to obtain the ketolactone (XL) through cyclisation of the acid (XLI) with polyphosphoric acid. A crystalline product, m.p. 159-60°, was isolated in



(XL) (XLII) (XLIII)

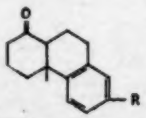
poor yield; to this the structure (XLII) has been tentatively assigned on the basis of infrared studies and the highly hindered nature of the carbonyl group. The unusual course of this ring-closure led us to investigate cyclisation of the acid (XLIII) under similar conditions (P.K. Ramachandran, D.Phil. Thesis, Calcutta University, 1960); this again afforded a mixture of 5- and 6-membered ketones as revealed through infrared studies, with the five-membered one predominating. Cyclisation of the acid (XLIV), however, leads to the expected 6-membered ketone. It is quite evident that acid-catalysed cyclisation and intramolecular acylation proceed along two different mechanistic pathways. The tacit idea that steric factor associated with *gem*-disubstituted grouping might be responsible for the for-

mation of cyclopentane rings appears to be untenable*. For synthesising diterpenoids having the characteristic 'C_2-OH' group, the following bicyclic acetoxyketones (XLV)[32g], and (XLVI)[32h] have been synthesised. Incidentally, it may be mentioned that these acetoxyketones might also serve as potential intermediates for the synthesis of triterpenoids.



(XLV) (XLVI)

Considerable success has been achieved towards the synthesis of diterpenoids, particularly with the ring C aromatic, and consequently having lesser number of asymmetric centres. Mention may be made in this connection of the synthesis of nimbiol,[32i, 33], ferruginol[34], sugiol[35], totarol[36], *dl*-podocarpic acid[32d,37], different isomers of desoxypodocarpic acid[32d], *dl*-dehydroabietic acid[38], and some of its stereoisomers[32j]. A close analysis of the methods developed for the successful synthesis of these compounds reveals some interesting common features: (*a*) cyclisation of phenethylcyclohexenes or their precursors, (*b*) a suitably substituted octahydrophenanthrenes, and (*c*) fusion of the ring A to the corresponding tetralin derivatives leading to octahydrophenanthrenes. As mentioned earlier, synthesis of the racemic form of *dl*-podocarpic acid was realised long back and its identity with the natural podocarpic acid has recently been established. All the successful methods developed by Bhattacharyya, Haworth, and King[37] follow the same procedure (*a*). A serious drawback of this method is lack of sufficient control on stereochemistry at C_1- and formation of *cis* and *trans* isomeric mixtures with respect to A/B rings, evidently due to comparative stability of the tertiary carbonium ion generated through protonation of the double bond of the cyclohexene ring. In fact, it has not been possible to develop the desired stereochemistry (e. g. C_{19}-Me: C_1-CO_2H *trans*) present in abietic acid systems from a suitably substituted phenethylcyclohexene derivatives. Next important development in this field is the synthesis of the tricyclic ketones[39].

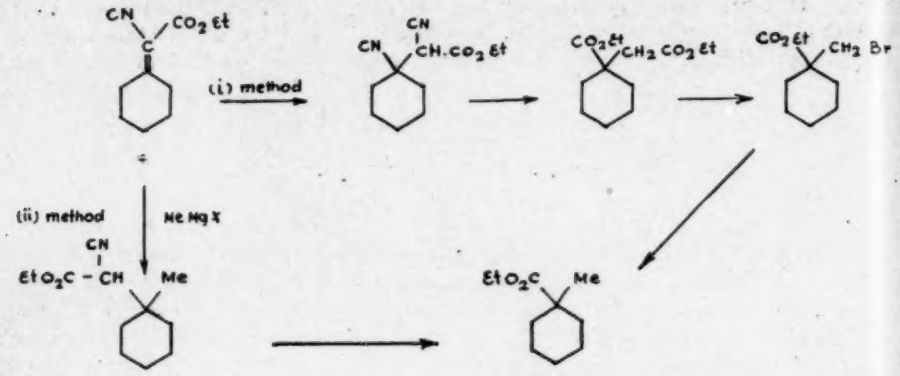


(XLVII : R=H or Pr^i)

The presence of the α-decalone system in these ketones was assumed to lead to the *trans*- ring junction. The next phase of synthetic studies stems with the development of suitable methods for converting carbonyl to *gem*-methyl-carboxyl function. Two methods[32c], complementary to each other, have been successfully developed utilising cyclohexanone as a model compound. It was expected that in the case of unsymmetrical tricyclic ketones,

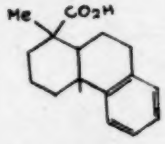
*The formation of the cyclopentane derivative is preferred as the formation of cyclohexane ring is difficult stereo-electronically (Spadling, *J. Amer. Chem. Soc.*, 1949, **71**, 1681).

(XLVIII) (XLIX) (L) (LI)



(LII) (LIII)

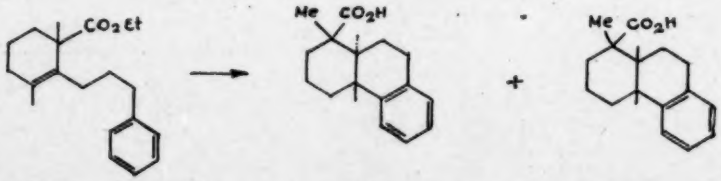
these two methods would ultimately lead to epimers at C_4 -because of the presence of the angular methyl group. Experiments in these directions led to the synthesis of an isomer of desoxypodocarpic acid (LIV) through the application of the method (*i*), but the second



(LIV)

method led to unexpected results which involved reduction of the double bond with the Grignard's reagent. This observation is a unique one as no β-hydrogen atom is available to explain the reducing property of methyl-Grignard reagent. This could only be explained by assuming that the intermediate transition complex had extracted hydrogen from ether which was present in the medium as solvent. An experimental verification of the hypothesis through the isolation of acetaldehyde via the hydrolytic fission of vinyl ether has so far failed. Incidentally, it might be mentioned that the tricyclic ketone (LVI) is a mixture of *cis* and *trans* forms (cf. N. N. Saha, D.Phil. Thesis, Calcutta University, 1953) with *cis* one predominating and this was established experimentally through oxidative degradation[4c].

The synthesis of two isomers[32d] of desoxypodocarpic acid has been achieved asshown below.

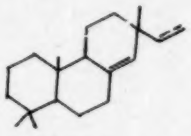


(LV) (LVI) (LVII)

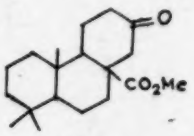
The acid (LVI) was utilised for the synthesis of *dl*-podocarpic acid through the introduction of 6-hydroxyl through acetylation. For the synthesis of the remaining isomer, the procedure (*c*) had to be adopted and the process followed the same pattern as was utilised for the synthesis of dehydroabietic acid. The synthesis of two other isomers of dehydroabietic acid has recently been reported[32j].

The synthesis of a tricylic compound (LVIII) with non-aromatic ring C and having functional groups, characteristic of the pimaric acid series has been achieved[41].

In the tetracyclic system, no notable achievement has been made so far. Announcement of the recent synthesis of phyllocladinic acid, a degradation product of phyllocladene, has been reported[42]. Synthetic studies by Cross and coworkers[43] on gibberellic



(LVIII)



(LIX)

acid have been quite prolific evidently because of its pronounced physiological importance as a plant-growth factor.

In the microcosm of organic chemistry represented by terpenoids, the diterpenoids occupy a conspicuous place by the side of sesqui- and triterpenoids as the grandeur of the entire arena is now quite apparent as a result of recent investigations from theoretical, mechanistic, phytochemical, and synthetic aspects.

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Stereochemistry of Rauwolfia and Biogenetically Related Alkaloids other than Yohimbane bases

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Last few years have witnessed extensive activities in the field of *Rauwolfia*[1,2] and related alkaloids[3]. The most interesting part of research in this field has been their stereochemical studies and biogenetic correlation[4,5,6]. This review concerns with our present day knowledge and the author's views on the stereochemistry of such alkaloids, listed in Tables I—III excluding yohimbane type already dealt with.

It is noteworthy that the tetracyclic indole compounds and tertiary α-and β-indoles have never been encountered in the same plant or same family whereas the former ones are found only in *Pseudo-cinchona* and yohimbehe bark (*Rubiaceae*), the latter type occuring exclusively in *Rauwolfia* species (*Apocynaceae*). The tertiary indole bases ($\alpha+\beta$ type) occurring in this family represent both yohimbane and heteroyohimbane types, which bear enough credence to Woodward's theory of their biogenesis[4]. His well-known postulate of the fission of the carbocyclic ring E in yohimbine (I) to an intermediate (II) with a free aldehyde group on one side chain, the mode of combination or condensation of which may lead to tetracyclic compounds (III), heteroyohimbanes (IV), and tertiary indoline bases (V), but the other two carbon atoms always appear as the side chain, is well established. These bases may be biogenetically related with the curare, e.g. mavacurine (VI), and apparently unrelated cinchona alkaloids[4], cinchonamine (VII) and cinchonine (VIII), as shown in Chart I.

*Stereochemistry of Heteroyohimbane Bases**

Heteroyohimbane bases, of which ajmalicine (IV) is a typical member, have three asymmetric centres C_3,C_{15}, and C_{20} common to yohimbine isomers (I). Thus, four types of ring-junction stereochemistry, viz., normal (C_3 and C_{15}–H= α, C_{20}–H=β) (IX), pseudo (C_3 and C_{20}–H=β-C_{15}–H= α), (X), allo (C_3, C_{15} and C_{20}–H= α) (XI), and epi-allo (C_3–H=β, C_{15} and C_{23}–H= α) (XII) are possible. Chemical, spectrophotometric, and pharmacological methods were applied for elucidation of the stereochemistry of these alkaloids.

Chemical Methods

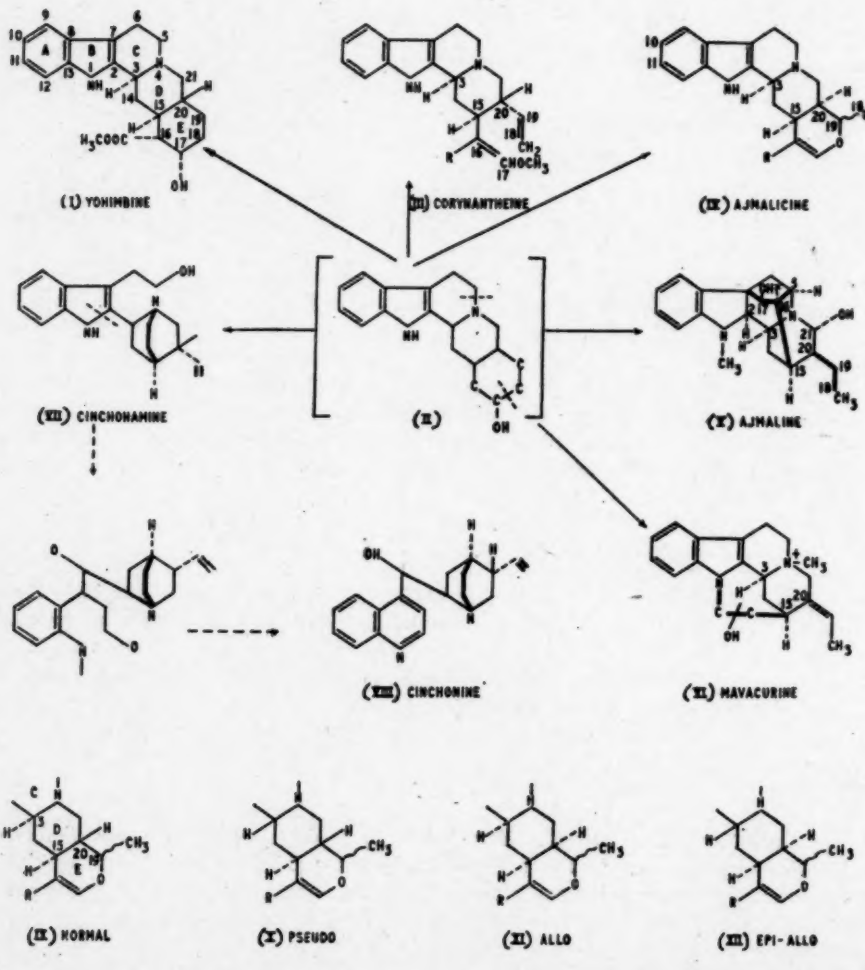
(*a*) *Oxidation of Ring* C *and Re-introduction of the* C_3*-asymmetric Centre with Stereospecific Reducing Agents.*—It has been established in yohimbine series[6] that catalytic hydrogenation or sodium borohydride reduction of the tetradehydro[13] or 3-dehydro compounds, obtained respectively by lead tetra-acetate and mercuric acetate oxidation,[6]

* A comprehensive review on Heteroyohimbines has been published by Dr. S. K. Talapatra, Dissertation for Premchand and Roychand studentship of the University of Calcutta, 1958.

leads exclusively to normal or preponderantly to allo products, depending on the *trans* or *cis* nature of the D/E ring system. On the other hand, reduction of the $\triangle^3$-compound with zinc and acid yields the corresponding C_3-H, β (e)-epimer[9]. The same reactions are also applicable to the heteroyohimbane bases[8,10,11,13]. Lead tetra-acetate oxidation of ring C being not of general applicability, palladium and maleic acid method was, however, applied with success. The relative rates of dehydrogenation with this reagent could also be used to differentiate between epi-allo compounds from pseudo. This rate is much slower for the former than the latter[8]. Mercuric acetate oxidation itself was proposed[9] as a diagnostic

CHART I

R = $COCH_3$



tool for ascertaining the axial or equatorial nature of hydrogen adjacent to a tertiary nitrogen atom. For, only those compounds having α-oriented axial C_3-H would be expected to undergo oxidation with this reagent. Wenkert and Roychaudhuri[12], however, have pointed out that it may be so with normal and pseudo compounds with unambiguous conformation, but not for allo and epi-allo systems, where C_3-H is always axial. Still it seems that this method serves to distinguish between α and β configuration of the C_3-H.

(b) Stability towards Mineral Acids: Formation of Dinitrophenylhydrazone Hydrochloride.—Chatterjee and Talapatra[13] have observed that heteroyohimbane bases with *trans* fused D/E ring system are capable of forming 2, 4-dinitrophenylhydrazone hydrochloride when the constituents are refluxed in presence of mineral acid[14], whereas *cis* D/E ring fusion imparts stability to the enol-ether linkage of the dihydropyran ring E towards its cleavage to aldehyde so that no such derivative is formed.

Spectrophotometric Methods

Infrared Spectrum Analysis.—Neuss and Boaz[15] developed spectrophotometric methods for differentiation between the *cis* and *trans* fused D/E ring systems in heteroyohimbanes. They found that in all *cis* cases the infrared spectrum in carbon disulphide showed a relatively simple band at 8.45μ, distinctly resolvable at 8.15, 8.32, and 8.45μ in *trans* cases. The bands corresponding to the C-C double bond in the infrared in chloroform is also distinguishable (6.14μ for *trans* and 6.19μ for *cis*).

Wenkert and Roychaudhuri[8] reported that the configuration at C_3 could be ascertained from the characteristic bands between the 3.4 and 3.7μ region in the infrared spectrum. Thus all compounds with α-oriented C_3-H exhibit two distinct peaks of medium intensity on the high wave length side of the major 3.46μ band and merely a shoulder at the same region appears for the β-oriented C_3-H.

Ultraviolet Spectrum Analysis.—The differential ultraviolet spectrum of tetrahydroalstonine *vs.* yohimbane exhibits two distinct bands, whereas a simple symmetrical band is shown by the corresponding differential spectrum of ajmalicine[15].

All the foregoing methods, when considered together, establish the stereochemistry of heteroyohimbane bases at ring junctions with reasonable amount of certainty (vide Table I).

Pharmacological Method

In an attempt to understand the relationship between the structure and hypotensive activities of *Rauwolfia* alkaloids, a novel, tentative correlation has been arrived at by the present author[16]. It has been observed that in yohimbine class of compounds, the greater the number of *trans* relationship between the absolute configurations of the vicinal, physiologically important asymmetric centres, weaker would be the hypotension by sympatholytic action only. With an increasing number of *cis* relationship among them, adrenolytic activity would develop in addition to sympatholytic property with the corresponding enhancement of hypotension. The ring-junction stereochemistry is considered more important for biological activity. Further, when the *cis*- and *trans*-related centres in any two isomers become equal, the one with *cis*-fused D/E ring system would have more pronounced and prolonged

activity than that with *trans* system and everything else remaining the same, C_3-α would have greater hypotensive activity than C_3-β.

An extension of this concept to the heteroyohimbane and anhydronium bases is quite revealing. It is necessary to assume on valid reasons that the replacement of the carbocyclic ring E with the heterocyclic one does not affect the biological activities much and to consider, obviously, the orientation of the C_{19}-methyl group instead of the asymmetric centre at C_{16} in yohimbane bases. Not only the newly developed concept can correlate the known hypotensive activities with the stereochemistry of such compounds providing indirect support to the assignments, but also the hitherto-unknown absolute configuration of the C_{19}-function could be predicted with confidence.

Stereochemistry of the Ring A-*Unsubstituted Heteroyohimbane Bases at* C_3,C_{15}, and C_{20}

Ajmalicine (IVa) on oxidation with lead tetra-acetate yields the naturally occurring tetradehydro compound, serpentine, whereas with mercuric acetate, the 3-dehydro compound is obtained. Now serpentine (XIIIa) or 3-dehydro-ajmalicine (XIV) on catalytic hydrogenation[10] or sodium borohydride reduction[13] in the latter case regenerates the original base. Reduction of the $\triangle^3$-compounds with zinc and acetic acid, on the other hand, affords 3-iso-ajmalicine (IVb), an epimeric compound, not yet encountered in nature[8]. From our present state of knowledge, ajmalicine should then have the more stable α-oriented C_3-H[9,11] and must belong to either normal or allo series. Undoubtedly, 3-iso-ajmalicine is its less stable C_3-epimer. That akuammigine (XVb) is also the C_3-epimer of tetrahydroalstonine (XVa) is proved[8] by its oxidation with palladium-maleic acid to the common tetradehydro compound, alstonine (XIIIb), another substance of natural origin.

Now alstonine (XIIIb)[14] and tetrahydroalstonine (XVa)[15] form 2, 4-dinitrophenylhydrazone hydrochloride unlike serpentine (XIIIa) and ajmalicine (IVa). So, the former pair was assigned the *trans*- and the latter, the *cis*-fused D/E ring system[13]. Molecular model experiments, the nature of the infrared bands at 8.15-8.45μ region, and the ultraviolet evidences support the conclusion[15]. Further, the characteristic infrared spectra at 3.4-3.7 μ region show that both these alkaloids should possess α-oriented C_3–H[8].

All the accummulated evidences prove that tetrahydrolastonine (XVa) is a *normal* and ajmalicine (IVa) is an *allo* compound. Necessarily, their C_3-epimers, akuammigine (XVb) and 3-iso-ajmalicine (IVb), should have *pseudo* and *epi-allo* form respectively. Besides infrared evidence, the rate of their dehydrogenation with palladium-maleic acid confirms this conclusions. Under identical conditions of arbitrary quenching of reaction, akuammigine undergoes 90% conversion, but 3-iso-ajmalicine remains unaffected.

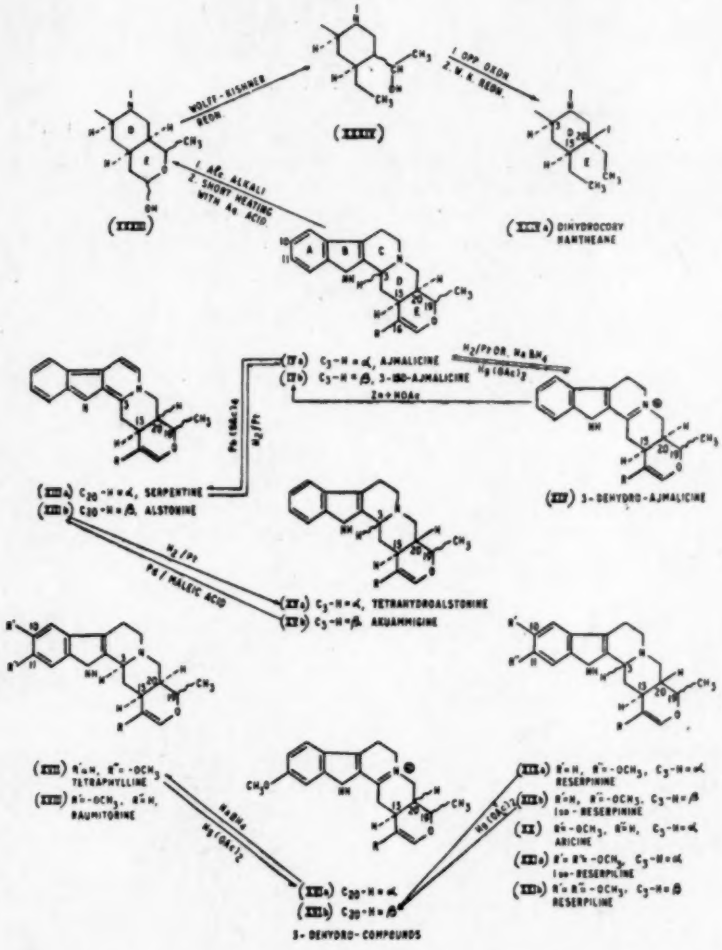
The infrared spectrum indicates that mayumbine belongs either to normal or allo series. So, it should be a C_{19}-epimer of either tetrahydroalstonine or ajmalicine[8]. From its reported[17] ajmalicine-like activity and by the application of the pharmacological method[16], mayumbine may be assigned allo-configuration.

Stereochemistry of the Ring A-*Substituted Heteroyohimbane Bases at* C_3, C_{15}, *and* C_{20}

The ring-junction-stereochemistry of the compounds, substituted with methoxyl group at C_{10},C_{11} or at both, should not differ from the unoxygenated compounds discussed so far, since such substitution is practically without any steric effect[15].

CHART II

$R=COCH_3$



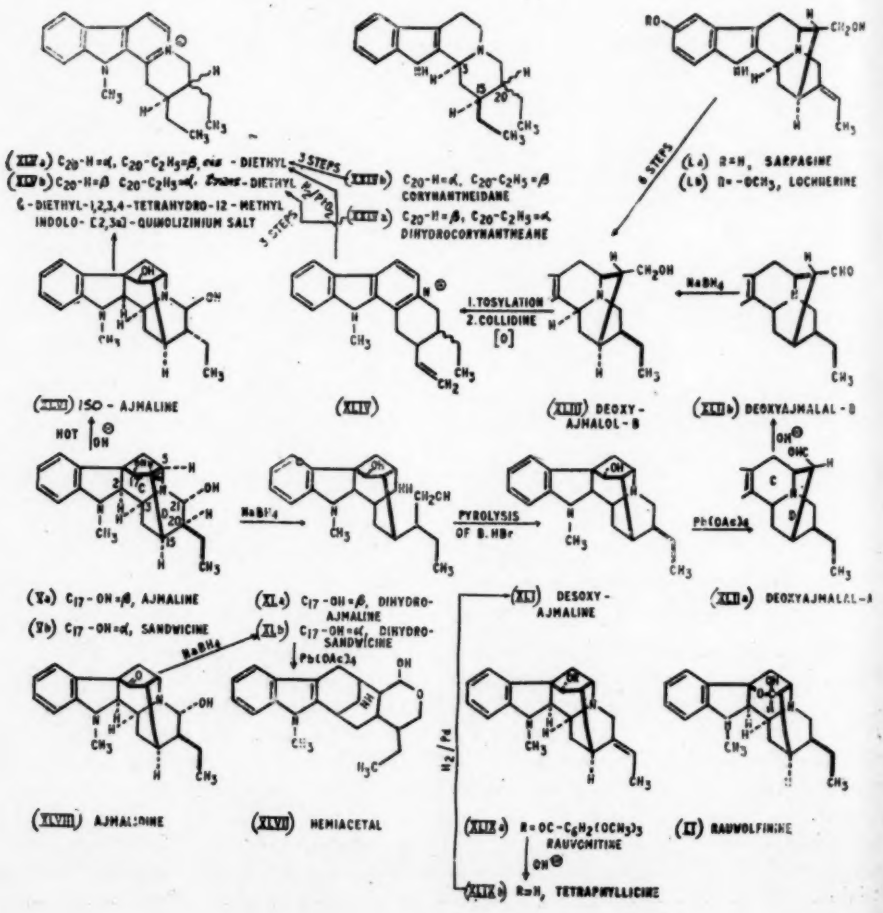
Djerassi *et al.*[11] from their studies on the C_{11}-oxygenated compounds have shown that 3-dehydrotetraphylline (XVIa), the mercuric acetate oxidation product of tetraphylline (XVII), is different from the common 3-dehydro compound (XVIb), obtained by the same method from reserpinine (XIXa) and isoreserpinine (XIXb). The last named alkaloids must therefore be the C_3-epimers, reserpinine[18] (XIXa) possessing the more stable conformation, whereas tetraphylline must differ from them with respect to one or more of the other centres.

Sodium borohydride reduction of 3-dehydrotetraphylline (XVIa) reconverts it to the original base (XVII). This fact together with the molecular rotation difference calculations

between the base and its 3-dehydro-compound establishes the α-configuration of its C_3-H. Tetraphylline should then belong to the normal or allo series.

Wenkert and Roychaudhuri[8] on the basis of the characteristic infrared bands at 3.4-3.7 μ region could classify some of the indole alkaloids broadly into two major groups, *normal* (IX) or *allo* (XI) and *pseudo* (X) or *epi-allo* (XII) compounds. Talapatra, Das and Chatterjee[18] by + or − reaction with D. N. P.. could recognise compounds having *trans* or *cis* D/E ring system[13] and hence belonging to normal and pseudor or allo and epi-allo series. Neuss and Boaz[15], on the basis of the narrow and intense bands at 6 to 7μ region of the summation infrared spectrum (in chloroform) of the corresponding methoxy-substituted 2, 3-dimethylindole and that of either tetrahydroalstonine (XVa) or ajmalicine (IVa), were able to differentiate the ring A-substituted heteroyohimbane bases belonging to either normal or allo structures, represented respectively by the standard substances used. The nature of the I.R. spectra of these alkaloids in

CHART II(a)


(XIV a) C20-H=α, C20-C2H5=β, cis - DIETHYL
(XIV b) C20-H=β C20-C2H5=α, trans - DIETHYL
6 - DIETHYL - 1,2,3,4 - TETRAHYDRO - 12 - METHYL INDOLO - [2,3a] - QUINOLIZINIUM SALT
3 STEPS
(XIII b) C20-H=α, C20-C2H5=β CORYNANTHEIDANE
(XIII a) C20-H=β, C20-C2H5=α DIHYDROCORYNANTHEANE
(I a) R=H, SARPAGINE
(I b) R=-OCH3, LOCHNERINE
I. TOSYLATION 2. COLLIDINE [Δ]
NaBH4
(XVI) ISO - AJMALINE
(XIV)
(XIII) DEOXY - AJMALOL - B
(XVI b) DEOXYAJMALAL - B
HOT
(Y a) C17 - OH=β, AJMALINE
(Y b) C17 - OH=α, SANDWICINE
(XI a) C17 - OH=β, DIHYDRO - AJMALINE
(XI b) C17 - OH=α, DIHYDRO - SANDWICINE
PYROLYSIS OF B. HBr
Pb(OAc)4
(XII) DESOXY - AJMALINE
(XII a) DEOXYAJMALAL - A
(XVIII) AJMALICINE
(XVII) HEMIACETAL
H2/Pd
(XIX a) R=OC-C6H2(OCH3)3 RAUVONITINE
(XIX b) R=H, TETRAPHYLLICINE
(X) RAUWOLFININE

carbon disulphide at 8.15-8.45μ region led to the same conclusion. All these independent approaches led to the same conclusion as regards the ring-junction stereochemistry of reserpinine (XIXa), aricine (XX), and isoreserpiline (XXIa). These are all *normal* compounds. Isoreserpinine (XIXb), the C_3-epimer[11] of reserpinine, must then have the *pseudo* configuration. Considering the latest infrared indications[15], tetraphylline (XVII) cannot but be an *allo* compound and so also raumitorine (XVIII), contrary to the earlier tentative assignment[3].

Reserpiline (XXIb), the only other compound left in this class, was tentatively assigned either *pseudo* or *epi-allo* ring system. The Lily research group[15] pointed out that this compound and isoreserpinine, although belonging to none, resembled *normal* more than *allo* series and were characterised by a broad band at 8.26μ. Since the latter alkaloid is definitely a pseudo compound, reserpiline should be expected to have the same ring junction stereochemistry. This was shown to be so by the Indian workers[18] by its formation of D. N. P. H. derivative. (Accordingly akuammigine, also a pseudo compound, should form the said derivative, which it does under refluxing condition (A. Chatterjee, personal communication) in difference to earlier report[3]. The assigned stereochemistry of reserpiline has also been supported by Pakrashi[16] from his studies on structure-activity relationship in this series. It is interesting to note that in accordance with this concept, the predicted weak sympatholytic activity of reserpiline in direct contradiction to its earlier reported higher potency and also the weak adrenergic blocking activity of isoreserpiline have found corroboration with the recent observations of the Basel group (A. Hofmann, private communication), thus showing the power of this new tool.

Stereochemistry of the C_{19}-methyl Group in Heteroyohimbane Bases

The pharmacological method[16] predicts that serpentine (XIIIa), ajmalicine (IVa), reserpinine (XIXa), and aricine (XX) should have α-oriented and alstonine (XIIIb), its epimeric tetrahydro compounds (XV), and reserpiline (XXIb) and isoreserpiline (XXIa) should have β-oriented C_{19}-methyl function (vide Table II). Mayumbine now considered to be the C_{19}-epimer of ajmalicine should then have the function β-oriented. Its activity, three times as much as that of the latter, however, is difficult to fit in since the hypothesis demands the relative degree of hypotension just the other way.

Stereochemistry of Corynantheine, Dihydrocorynantheine, and Corynantheidine

The chemistry and stereochemistry of these alkaloids have already been surveyed[3]. Only a brief account will be presented to include the salient features leading towards their stereochemical assignment as indicated in Chart III.

Corynantheine (III) or its hydrogenation product, dihydrocorynantheine (XXIIa), and corynantheidine (XXIIb) could be converted[20] to the oxygen-free compounds, dihydrocorynantheane (XXIVa) and corynantheidane (XXIVb) through dihydrocorynantheal (XXIIIa) and corynantheidal (XXIIIb). The reaction sequence involves saponification, decarboxylation, acid hydrolysis, Wolff-Kishner reduction and in case of corynantheine, hydrogenation of the penultimate product, corynantheane (XXV), none of which is expected to affect the asymmetric centres at C_{15} and C_{20} in analogy to yohimbine isomers[6].

TABLE I

Heteroyohimbane bases.

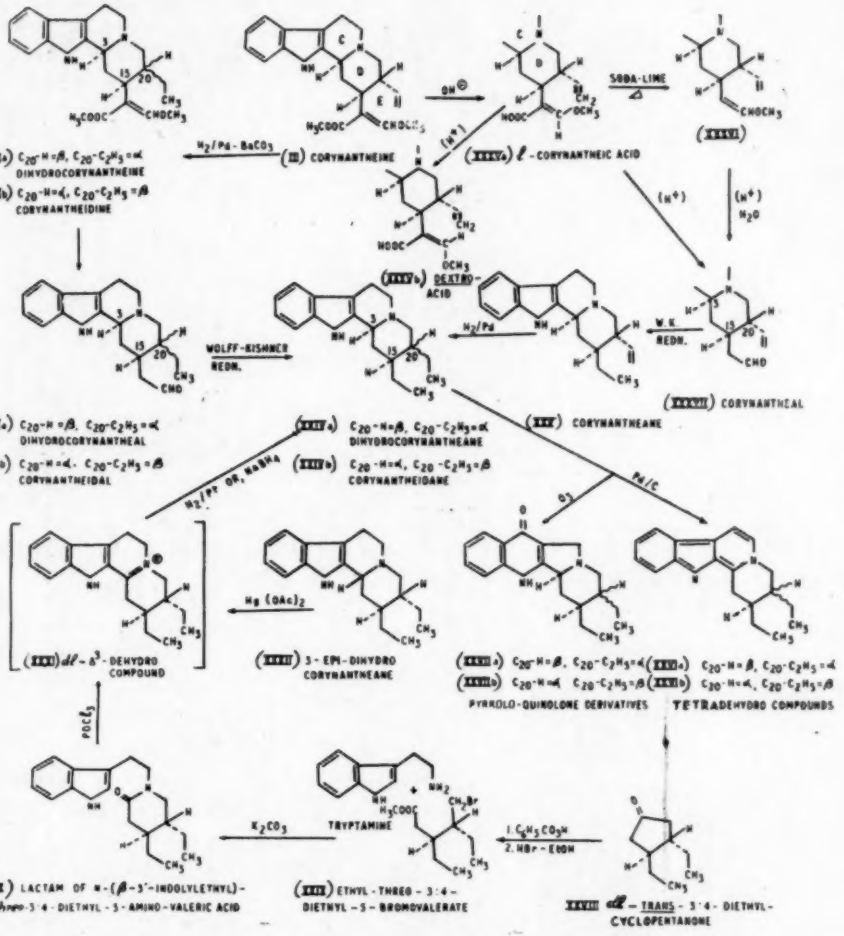
No.	Name of alkaloid.	M.P.	α_D.	Stereochem. at ring junctions.	Absolute configuration of C_{19}-methyl (tentative).
	A. Ring A-unsubstituted compounds ($C_{21}H_{24}O_3N_2$).				
1.	Ajmalicine (δ-yohimbine)	240-52°	—58,1°(C)	Allo	α
2.	Tetrahydroalstonine	230-32°	—98°(C)	Normal	β
3.	3-Isote-tetrahydroalstonine (akuammigine)	113°	—42°(E)	Pseudo	β
4.	Mayumbine	216°	—68°(P)	Allo	β
5.	3 Iso-ajmalicine			Epi-allo	α
	B. Ring A-substituted at C_{11} with OMe ($C_{22}H_{26}O_4N_2$).				
6.	Reserpinine	238-39°	—117°(C)	Normal	α
7.	Isoreserpinine	225-26°	—5°(P)	Pseudo	α
8.	Tetraphylline	220-23°	—73°(C)	Allo	
	C. Ring A-substituted at C_{10} with OMe ($C_{22}H_{26}O_4N_2$).				
9.	Aricine	189°	—58°(E)	Normal	α
10.	Raumitorine	138°	—69°(C)		
	D. Ring A-disubstituted at C_{10} & C_{11} with OMe ($C_{23}H_{28}O_5N_2$).				
11.	Reserpilime	205-207°	—38°.4(E)	Pseudo	β
12	Isoreserpiline	212°	—82°(P)	Normal	β
	E. Quaternary anhydronium bases ($C_{21}H_{20}O_3N_2$)				
13.	Alstonine	300°	—	*Trans*	β
14.	Serpentine	158°	+188°†	*Cis*	α
15.	Serpentinine. ($C_{21}H_{22}O_3N$)	265	+52°(M)		Not discussed due to uncertain structure.

*Not yet found in nature.
†B. HCl in water.

C=chloroform, E=ethanol, M=methanol, and P=pyridine.
Reference Nos. 2 & 3 embrace all the tables except those mentioned.

The diastereoisomeric products[20] of (XXVIa), obtained by lead tetra-acetate oxidation of dihydrocorynantheane and corynantheidane, prove these to be epimeric at C_{15} and C_{20}. On the basis of molecular rotation differences between these two desoxy compounds (XXIVa & b) and their respective ozonolysis products (XXVIIa & b) as well as the tetradehydro derivatives (XXVIa & b), it is concluded that both the original desoxy compounds have α-configuration at C_3-centre.

CHART III



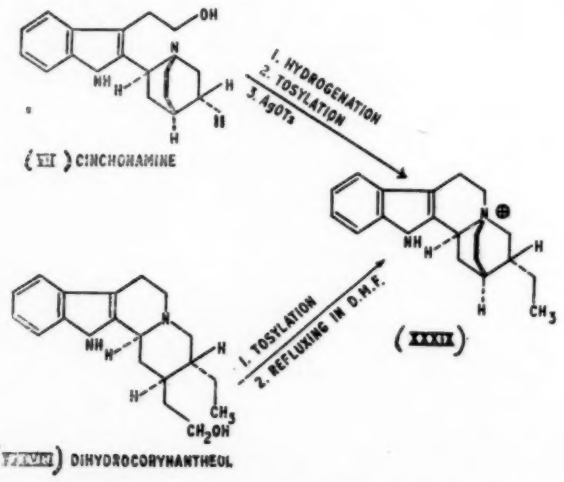
The stereospecific synthesis[21] of *dl*-dihydrocorynantheane, starting from *trans*-3,4-diethylcyclopentanone (XXVIII) through (XXXI), unambiguously establishes the *trans* configuration of dihydrocorynantheane at C_{15} and C_{20}. Obviously, in corynantheidane (XXIVb) these two centres must have *cis* arrangement. The catalytic hydrogenation of the $\triangle^3$-product (XXXI) in the last stage of synthesis as also the recently reported[22a] sodium borohydride reduction of the mercuric acetate-oxidation product of 3-epi-dihydrocorynantheane (XXXII), synthesised from cinchonine (VIII) and characterised as picrate, (m. p. 207°–208°), settles the C_3-α-orientation of dihydrocorynantheane (XXIVa). Further support to the assigned configurations was adduced by its conversion[5] from ajmalicine (IV) through (XXXIV) (vide Chart II.)

Undisputedly, corynantheine has *trans* arrangement at C_{15} and C_{20} but its configuration at C_3 remains uncertain because of the notoriety[6] for inversion of the Wolff-Kishner reduction method employed during its conversion through corynantheal (XXXVII) to the desoxy bases (XXV) & (XXIVa). The mode of formation of corynantheal from corynantheic acid (XXXVa), both by the drastic alkali treatment followed by hydrolysis or by acid hydrolysis alone[19b], leaves little doubt[21] as to the stable *cis-trans* (normal) configuration at C_3, C_{15}, and C_{20} of corynantheal (XXXVII) and corynantheine (III), from which the acid (XXXVa) is obtained by saponification under condition insufficient for epimerization.

The interesting change of *laevo*-corynantheic acid (XXXVa) to the *dextro*-acid (XXXVb) has been interpreted by Janot and Goutarel[19b] as due to geometrical isomerism[21].

With the conversion[5] of ajmalicine and corynantheine (*vide supra*), cinchonamine (VII) and dihydrocorynanthel (XXXVIII) to their common intermediates (XXIVa) and (XXXIX) respectively as also by the synthesis of dihydrocorynantheane (XXIVa) from cinchonine (VIII) or of 10-methoxydihydrocorynantheane from quinine or conversion of cinchonidine to dihydrocinchonamine[22b], together with the established absolute configurations of cinchona bases[23], which constitute a large number of alkaloids, yohimbe and cinchona are found to be related. Such biogenetic possibility was already pointed out by Goutarel *et al*[24]. Besides, all the evidences conclude that the absolute configuration of C_{15}-H is α and the same is for all indole and biogenetically allied alkaloids[5,25]. This led Wenkert and Bringi[5] to suggest shikimic acid rather than 3, 4-dihydroxyphenylalanine[7] as the phytogenic precursor of ring E in yohimbine alkaloids.

In view of the above finding, it may be pointed out also that of the two alternative configurational possibilities of corynantheidine (XXIIb) (both C_{15} and C_{20}-H, α or β), that with the C_{15}-H, α should be the correct one.



Stereochemistry of Tertiary Indoline Bases: Sarpagine and Lochnerine

Indole alkaloids, sarpagine (La) and its methyl ether[26], lochnerine (Lb)[27] will now be discussed along with the tertiary indoline bases, to which they are closely rela-

ted both biogenetically and from the stereochemical point of view. Of the alkaloids listed in Table II, not much is known about sandwicensine, mauiensine and semperflorine, except that they belong to this class of compounds, and hence are left out of consideration.

TABLE II

Tertiary indoline bases and their indole analogues.

No.	Name of alkaloid.	Mol. formula.	M.P.	α_D.
1.	Ajmaline	$C_{20}H_{26}O_2N_2$	158-60°	+128°(C)
2.	Isoajmaline	,,	264-66°	+72°.8(E).
3.	Sandwicine[7]	,,	(Gelatinous)	+180°(C)
4.	Ajmalidine	,,	241-42°	—
5.	Rauwolfinine	$C_{20}H_{26}O_2N_2$	235-36°	−34°.7(E)
6.	Tetraphyllicine (=Serpinine[27a])	$C_{20}H_{24}ON_2$	320-22°	+21°(P)
7.	Rauvomitine	$C_{30}H_{34}O_5N_2$	115-17°	−173°.4(C)
8.	Sandwicensine[7]	$C_{19}H_{22}N_2O.CH_3OH$	260-62°	−56°(M)
9.	Mauiensine[7]	$C_{20}H_{26}N_2O$	240-42°	+184°(M)
10.	Semperflorine	$C_{21}H_{26}ON_2$	295°	—
11.	Sarpagine	$C_{19}H_{22}O_2N_2$	363-64°	+55°(P)
12.	Lochnerine	$C_{20}H_{24}O_2N_2$	200-201°	+50°(E)

Ajmaline, Isoajmaline, Ajmalidine and Sandwicine

Ajmaline (Va), whose structure has been established through the extensive pioneering work of Anglo-Indian group[3] of workers and by Woodward[4], is a complex compound[2,3] with asymmetric centres at C_2, C_3, C_{15}, C_{20}, and C_{17}. Yet the caged ring structure offers some advantage because the stereochemistry at five of them, viz. C_2, C_3, C_{15}, C_{16}, and C_5, once settled would be fixed and be common to all the bases with such a structure.

For biogenetic reasons discussed already, the C_{15}-H must be α-oriented and the caged ring structure requires C/D rings to be *cis*-fused in analogy with the formation of quaternary bases in reserpine series[2]. This has been demonstrated by Talapatra and Chatterjee[28] through their molecular model studies of sarpagine of similar ring system. C_3-H was shown to be equatorial with respect to ring C and the failure of sarpagine to produce 3-dehydro derivative with mercuric acetate, which supposedly requires an axial C_3-H[9,12], has been cited in support.

Chemical evidences leading to the stereochemical assignment of ajmaline (Va) has only been advanced recently by the American workers[29]. Desoxyajmaline (XLI) on lead tetra-acetate oxidation yielded deoxyajmalal-A(XLIIa). The latter epimerized to deoxyajmalal-B (XLIIb), which on reduction with sodium borchydride afforded deoxyajmalol-B (XLIII), m.p. 217-18°, $(\alpha)_D$ -7°. Its *O*-tosylate on refluxing with collidine for 2 hours suffered fission; aero-oxidation to give (XLIV), isolated as perchlorate (XLIV) on hydrogenation over Adams' catalyst, yielded 1-*cis*-diethyl-1,2,3,4-tetrahydro-12-methyl-indolo-[2,3a]-quinolizinium perchlorate (XLVa), m. p. 212-13°, $[\alpha]_D$−27°. The same compound was obtained from corynantheidane (XXIVb) of the established stereochemistry through *N*(a)-methylation, pyrolysis, and dehydrogenation. This correlation definitely

establishes the stereochemistry of the hexacyclic system and *C*-ethyl in ajmaline as shown in (Va).

By the same series of reactions from isoajmaline (XLVI), the *d-trans*-diethyl derivative (XLVb), m. p. 201-202°, $[\alpha]_D$+16°, is obtained to which dihydrocorynantheane (XXIVa) could also be degraded as from corynantheidane, thus establishing isoajmaline to be the C_{20}-epimer of ajmaline. This was already proposed[30] from the isomerization of the former to the latter by the action of heat or hot ethanolic alkali.

The carbinolamine hydroxyl at C_{21} in ajmaline is believed to be *trans* to the *C*-ethyl function by the Ciba group[29]. It has been explained (W. I. Taylor, private communication) that being the carbinolamine system, epimerization of the *C*-ethyl from one to the other must proceed *via* the anion of the ring *opened* form and the hydroxyl will preferably take up the least hindered position. The *trans* arrangement between the hydroxyl and *C*-ethyl functions would probably be the most favourable to avoid interaction in them. The same arguments hold good for isoajmaline (XLVI) in which these two groups should be expected also to be *trans* related. It may be pointed out that the possibility of isoajmaline being the C_{21}-epimer of ajmaline rather than C_{20} is discounted on the ground that the desoxy and dihydro compounds from the two alkaloids still show isomerism and that both of them yield the same decarbonoajmaline[3]. But this observation could not exclude the possibility of isomerism due to both the centres.

TABLE III

Tetracyclic indole bases.

No.	Name of alkaloid.	Mol. formula.	M.P.	$[\alpha]_D$.	Ring-junction stereochemistry.
1.	Corynantheine	$C_{22}H_{26}O_3N_2$	165-66°	+28.8°(M)	Normal
2.	Dihydrocorynantheine	$C_{22}H_{28}O_3N_2$	177-77.5°	+26.2° (M)	,,
3.	Corynantheidine	Do	125°	−171°(M)	Allo

While working with sandwicine (Vb), another isomer of ajmaline, Gorman *et al.*[7] observed that like dihydroajmaline (XLa), dihydrosandwicine (XLb) also underwent lead tera-acetate oxidation and the resulting aldehyde spontaneously cyclized to the hemiacetal (XLVII). Since no asymmetric centre other than C_{17} is involved, dihydroajmaline and dihydrosandwicine must necessarily be the C_{17}-epimers and possibly so also the original bases. This conclusion was borne out by the sodium borohydride reduction of ajmalidine (XLVIII)[31,32] to dihydrosandwicine (XLb), establishing at the same time the configuration of the C_{17}-hydroxyl group in ajmaline and sandwicine. Since sodium borohydride reduction of the carbonyl group would normally yield the stable compound, should these alkaloids have been the C_{21} rather than C_{17}-epimers one would have expected the same product from both of them. Moreover, the reduction of the ketone to dihydrosandwicine proves that in sandwicine the C_{17}-hydroxyl group should be more stable α-equatorial and in ajmaline it should be β-axial. Here again, the possibility of isomerism both at C_{17} and C_{21} could not be rigorously excluded. But since the orientation of C_{20}-ethyl in both of them should be the same and greater thermodynamic stability requires the C_{21}-hydroxyl *trans* to this

group[29], both ajmaline and sandwicine should have identical stereochemistry at these centres and they are definitely the C_{17}-epimers.

Tetraphyllicine and Rauvomitine

Tetraphyllicine, obtained from hydrolysis of rauvomitine (XLIXa), on catalytic hydrogenation affords desoxyajmaline (XLI)[11,32]. These facts enable one to deduce the stereochemistry of tetraphyllicine as depicted (XLIXb) except that of the ethylidene side chain. The C_{17}-hydroxyl is assigned α-equatorial because the heavy substituent of rauvomitine at C_{15}-should have more stable equatorial orientation and the condition of its hydrolysis is not strong enough for epimerization at this centre. Further, since catalytic hydrogenation of tetraphyllicine to desoxyajmaline[11] (XLI) should not disturb this centre, the latter would have the same orientation also. The drastic conditions used during its conversion from ajmaline[30], inversion of the axial C_{17}-hydroxyl to the more stable equatorial one in desoxyajmaline (dihydrotetraphyllicine) is not hard to expect.

Sarpagine and Lochnerine.—The first attempt to determine the stereochemistry of sarpagine was made by Talapatra and Chatterjee[28] on the basis of conformational analysis (*vide supra*). Recently, Bartlett, Sklar and Taylor[33] could advance convincing proof of its stereochemistry as indicated (La) with the exception of the ethylidene function. Through a series of reactions involving catalytic hydrogenation of the ethylidene side chain, acetylation of the primary alcohol, tosylation and cleavage of the phenolic hydroxyl, N-methylation and hydrolysis they could convert sarpagine to deoxyajmalol-B(XLIII) of established stereochemistry. Hence that of lochnerine (Lb) follows.

Rauwolfinine.—The stereochemistry of rauwolfinine[34,35] (LI) has been elucidated. It has the same steric feature at $C_{3,5,15,16,20}$ as that in ajmaline.

In conclusion, it may be said that the stereochemical studies of tertiary indoline bases are by no means complete and the interest in this much studied field of *Rauwolfia* still remains alive. It is also of interest to note that the present author has been able to correlate the hypotensive activities of tertiary indoline and allied bases with their stereochemistry which will appear shortly elsewhere.

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On the Role of Synthetic Chemistry in Chemotherapy

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Organic chemistry has advanced considerably during the last 50 years. The creative function of organic chemistry is supplementing Nature to help mankind in maintaining health and combating disease. Systematic research on medicaments has much widened the frontiers of Science. With the advance of knowledge in natural sciences, studies on the composition and constitution of the natural products were undertaken. Hundreds of alkaloids (about 950) are known to-day and yet according to Willaman and Schubert[1] only 2% of all species of plants has so far been tested for their alkaloid content. Many of the known alkaloids have been synthesised. The historic development of our knowledge in the field of alkaloids is summarized in Table I.

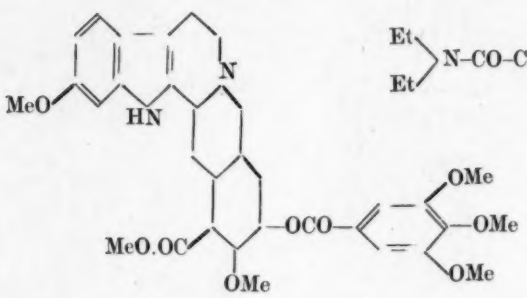
TABLE I

Alkaloid.	Isolation.	Structure evaluation	Synthesis.
Morphine	1817 (1804)	1927	1952
Strychnine	1818	1947	1954
Quinine	1820	1909	1944
Nicotine	1828	1895	1900
Atropine	1834	1898	1904
Papaverine	1847	1886	1909
Aconitine	1856	..	..
Cocaine	1860	1898	1902
Ephedrine	1885	1909	1925
Lobeline	1920	1928	1929
Ergotamine	1922	1951	..

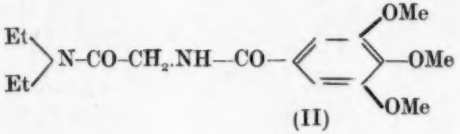
While it took over a century to synthesise these few alkaloids, synthetic organic chemistry has made rapid progress and new synthetic drugs keep on appearing in increasing numbers at frequent intervals. One of the latest biologically active alkaloids is reserpine, first isolated in 1952 from the Indian plant *Rauwolfia serpentina*, and synthesised in 1956. It is an indole derivative (I) containing a trimethoxybenzoyl grouping interlinked through a complex cyclic chain to the indole part of the molecule.

The observation of Crongeim *et al.*[2] on the sedative action of trimeglamide, trimethoxybenzoyl glycine diethylamide (II), on human subjects tends to show the role of modern techniques in the synthesis of structural analogues of natural drugs. A survey of literature

would show that many analogues of alkaloids have been synthesised by the organic chemists and their specific biological activities established by collaboration with the biologists.



(I)
Reserpine



(II)
Trimeglamide

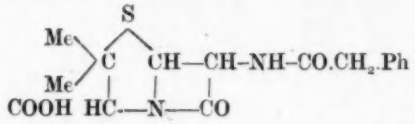
The local anaesthestic, cocaine, the constitution of which was established in 1898, was practically replaced in 1905 by the simpler substance, procaine. The alkaloid, morphine, is now being replaced to an extent by pethidine, the activity of which was revealed after thirteen years of establishment of the structure of morphine[3]. All these examples tend to suppport the suggestion that synthesis for its own sake may be continued on a planned basis and this may reveal products of outstanding utility in health and disease.

Newer Advances

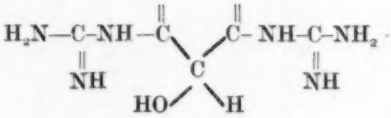
With the development of our knowledge in chemistry (particularly organic chemistry) and with the expansion of the methods of technique in pharmacology, attempts for synthesing newer products having no relation with the natural analogues have been made with significant success in several directions. Work in the fields of antipyretics and analgesics is too well known. Similarly, hypnotics, sedatives, and anticonvulsants were discovered in barbituric acids, amides, ureides, and hydantoins. The interesting findings of vasoactive response of nikethamide and cardiazole are a distinct contribution of synthetic chemists to medicine. More ingenuity came to be borne on such investigations since the introduction into bacteriology of staining methods using organic dyes. Ehrlich in 1881 described the staining of bacteria with methylene blue and in the year 1891 he demonstrated the activities of methylene blue on malaria parasites. Quinine has been in use as a chemotherapeutic agent against malarial infections. Once it was realized that a synthetic product might be effective in combating bacteria as well as protozoa, development of chemotherapy proceeded rapidly and synthetic drugs, which had no relation with the naturally-occurring biological agents, were introduced in clinical practice. In this connection, chiniofon and iodochlorohydroxyquinoline may be mentioned as the earlier agents introduced for the treatment of amoebic dysentery which, however, still needs a better and more effective drug.

The failure of quinine to cure all forms of malaria gave an impetus to extensive studies aimed at the discovery of a product better than quinine; plasmochin was introduced in 1924 and atebrin in 1933. Introduction of the potent antimalarial, paludrine, during

the war period was a triumph of modern synthetic chemistry in the field of drug design. The current drug of choice is, however, chloroquine. Chemical structures of all these products would, however, indicate that synthetic chemists have been successful in preparing products with equivalent or even better biological activity, much simpler in constitution than those produced by nature.



(III)



(IV)

In spite of these spectacular advances, the progress in combating infections of bacterial origin was slow in the early stages. The synthesis of prontosil by Mietsch and Klarer in the Elderfield laboratory of Baeyer and its efficacy in the streptococcal infection, as demonstrated by Domagk in early thirties of this century, opened up a new field for synthetic chemists. Everyone is now familiar with sulfa drugs that have helped in controlling the scourges caused by many pathogenic bacteria. While treatment of various diseases with synthetic chemotherapeutic agents was playing a predominant role in the medical field, the discovery of the powerful antibiotics, penicillin, tetracycline, aureomycin, and streptomycin, brought the substances of natural origin in limelight again. The speciality of penicillin lies in its four-membered lactam ring condensed with a sulphur containing five-membered ring (III) and that of streptomycin in its peculiar guanidine structure (IV). These antibiotics possess a wide spectrum of biological activity; the former is effective against gram-positive and the latter against gram-negative organisms. Taking advantages of easy screening methods, now available, the synthetic chemists have produced newer derivatives of sulphonamide to combat infections of the former type, and simpler compounds like *para*-aminosalicylic acid, isonicotinic acid hydrazide, and sulphones to control the latter. Thus it is found that natural compounds are being successfully substituted by synthetic products.

Problems to be Solved

Infectious diseases are now controlled in the West largely by public health measures. It is expected that in our country also, with the improvement of our economic level and with the maintenance of healthy conditions of our environments, incidence of infectious diseases will be reduced appreciably. In the developed countries of the world, heart disease (to which vascular lesions of the central nervous system are added) and cancer are responsible for the highest number of deaths. Treatment of these ailments has become a challenge to those interested in evolving synthetic medicaments. Difficulty in the production of anticancer drugs is due to the fact that neither the mode of formation of cancer cells, nor the law of their spreading is clearly known. In cancerous growth the rate of cell division (mitosis) is abnormally high. Either the formation of the abnormal cells or the mitosis has to be checked. Difficulty in evolving any synthetic medicament in this case, is that one has to deal not

with an invading pathogenic organism foreign to the body, but with the host's own tissues. Undesirable growth has to be controlled without affecting the normal cells. It is known that the change from normal to malignant transformation may be stimulated by numerous chemical, physical, and biological agents, but the nature of this change is not very clear. The nucleus of the cell contains polymers composed of nucleotides, known as deoxyribonucleic acid (DNA) and it is believed that a derangement of the native DNA is the cause of cancer. Prevention of such derangement becomes the problem.

The chemotherapy of cancer is a very complicated problem and more than 40,000 chemicals are screened every year in the United States of America for anticancer activity. Numerous compounds of varied nature have been and are being synthesised for biological testing. Different compounds in the nitrogen mustard series have been studied. The first compounds used against cancer was methyl-bis-(β-chloroethyl) amine. Substitution of the methyl group in this compound by various other groups, particularly those containing peptide linkages, have been found to combine with most cell constituents, and to inhibit many enzyme systems including choline oxidase, choline esterase, and pyruvic acid oxidase.

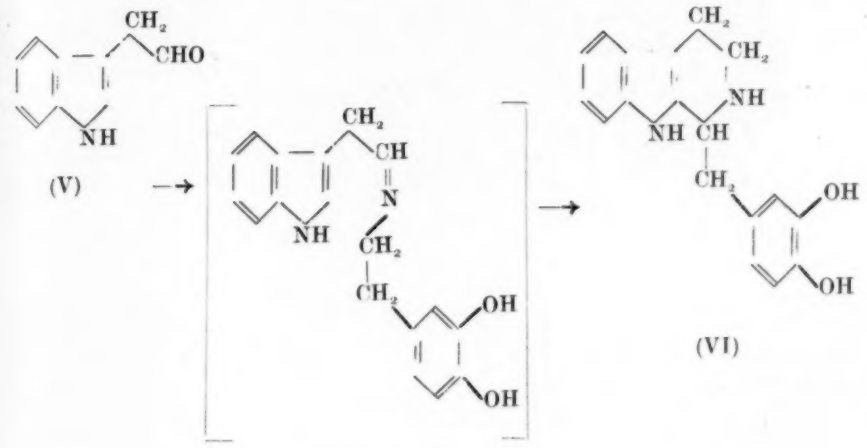
Products of divergent nature are being tried in search for a suitable compound to combat malignant growth in bone, skin, glands, and heart or the tumours of lipoid processes, but none has so far been found to be an ideal chemotherapeutic agent. In Hodgkin's disease, lymphosarcoma, and lymphocytic leukemia interesting observations are on record from a study with ethylenimines. The product that has been more extensively studied is 2, 4, 6-tris-(ethylenimino)-*s*-triazine. This compound, commonly known as TEM, has a profound inhibitory action on the progress of human cancer; but with nitrogen mustard the cancerous cells tend ultimately to be refractory to this compound. It is of interest to note that the antimalarial (supazine), worked out in this Institute, is also a triazine derivative, but it has not been tested for anticancer activity.

Among the natural products colchichine derivatives have been tried, but the problem lies in controlling the formation and regulation of cell and its constituents. It has not yet been elucidated how the change from the normal to the malignant cell takes place.

Brilliant successes have been achieved in the treatment of bacterial, protozoal and spirochaetal infections, but we do not know the fundamental biochemistry of the microorganisms, the nature of the various enzymatic reactions in the system. nor anything about their integrated functioning in the living cell. Although we have been able to control the infectious diseases and prolong life expectancy, we are in difficulty in controlling the disorders produced by virus infections or cancer or, with heart diseases, which are responsible for the maximum number of deaths in the developed countries of the world. Attempts are being made to synthesise chemical compounds to combat these conditions also.

In order to deal with the treatment of heart diseases, one has to consider the biochemical reactions that are going on in the system. The essential phases of cardiac metabolism are energy production and energy liberation. The former involves oxidation of our food materials, and the latter relates more to protein functioning and various enzyme reactions. We do not know all changes that are going on *in vivo*. We cannot also fix our diet, environmental conditions, and other habits, and as such who knows whether the breakdown products of our heterogeneous food may be the factors in controlling the physiology of the system. Many pressor amines are being formed, oxidised and/or converted to

different products to exert one or other physiological phenomenon. Our food protein, casein, contains an amino-acid, tryptophan, which is known to form vaso-active (pressor) amines-tryptamine or serotonin. Under the influence of the monoamine oxidase (as enzyme present in liver) they may undergo oxidation to aldehyde of the type (V). This aldehyde may easily react with the naturally-occurring monoamines (for example, dopamine) to give rise to products (VI) bearing a close relationship to indoles to which group many psychotropic drugs like harmine (VII), yohimbine (VIII), and reserpine (I) belong.



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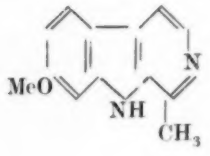

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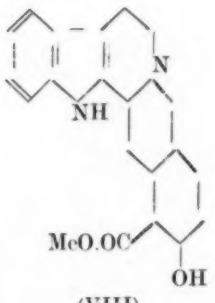

(VIII)

As a matter of fact, tryptophan has been converted in the laboratory to afford harman. In nature various enzymes play a role in many biochemical reactions and help in the formation of different components in the system to exert pharmacological action. Recent discoveries have revealed that the naturally-occurring active substances, vasopressin, insulin, gulcagon, and hypertensin, are compounds of peptide nature. Thus, the synthetic chemists find new fields for investigation. As a matter of course, organic chemists have already synthesised a number of compounds that are helping in producing a prolonged lowering of the tension. Amongst these mention may be made of chlorpromazine[4] (phenothiazine derivative), hydroxyzine (diphenylmethane derivative) hydrazino-phthalazine, mephenesin (propane-diol derivative) and hydrochlorothiazide. These are products of diverse

nature, but they all exert therapeutic action in the same disorder. Influence of a drug in man as a whole would be of complicated nature, but the modern tracer methods may help the biologists in offering their suggestion to chemists for the synthesis of novel structures to reveal newer chemotherapeutic compounds.

Synthetic chemistry is receiving profound significance from the rapidly progressing elucidation of biosynthesis in Nature, and newer developments in operating science. We now know that hormones formed in our body can influence the psychic and mental behaviour. We know that our food proteins provide both stimulants as well as depressing agents. It is difficult to predict any future development. We have already discovered many drugs to mitigate our miseries, but the aspiration of synthetic chemists is now to control the symptoms of ageing. With the help of the physical and biological aids, organic chemists may help in the isolation of products that play decisive role in proper functioning of the body and subsequently, in the production of chemotherapeutic products to control various disorders that are being noticed amongst people living under stress and strain of modern civilization.

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Investigation of a Kuweit Crude Oil

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In this paper a short review is given of the principles applied in the graphical statistical analysis of crude oil fractions. Applications are shown in the characterization of a Kuweit crude. The correlation between distinct physical constants and the chemical structure of a number of fractions of the crude is demonstrated by comparing experimental physical data with data, predicted by means of proper relations[1].

Principles of Graphical Statistical Analysis of Mineral Oils

Mineral oils consist chiefly of complicated mixtures of hydrocarbons; distinct amounts of sulphur, nitrogen, and oxygen compounds and small quantities of organo-metallic compounds may be present as well. The hydrocarbons belong to the following groups:

(*a*) The paraffins, saturated noncyclic molecules in which branchings may be present.

(*b*) The naphthenes, consisting mainly of saturated cyclopentane and cyclohexane derivatives.

(*c*) The aromatics.

Olefinic hydrocarbons are generally absent in natural crudes; they may play an important role in cracked products of any kind.

For the low-boiling fractions (up to the gasoline range) the distinction between these groups is quite sharp. Application of modern separation methods (distillation, chromatography, etc.) enables a reliable quantitative separation of the groups mentioned; the isolation and identification of *individual* hydrocarbons, however, requires elaborate and time-consuming research. Complete separations have been executed in a few cases only[2].

In mineral oil fractions of higher molecular weight the total number of different hydrocarbon molecules is extremely high and with a few exceptions the separation and identification of individual molecules are not possible by the existing methods. In the hydrocarbon molecules paraffinic, naphthenic, and aromatic elements may be linked together and therefore these molecules may possess paraffinic, naphthenic and aromatic properties in a ratio which to a certain extent will be determined by the proportion of the respective structures. Thus, to solve the problem of analysis of these fractions it is necessary to deal with the oil fractions *statistically*[3]. These are considered to be built up of a limited number of structural elements which are related to an *average molecule*, a hypothetical molecule, representing the average nature of all the individual molecules present in the mixture.

The following quantities are normally taken into account:
R_N, the number of rings per average molecule in naphthenic structure.
R_A, the number of aromatic rings per average molecule in aromatic structure.
$R_T = R_A + R_N$, the total number of rings per average molecule.
$\%C_N$ = %carbon atoms present in naphthenic structure.
$\%C_A$ = %Carbon atoms present in aromatic structure.
$\%C_P$ = %Carbon atoms present in paraffinic structure.
$\%C_R = \%C_A + \%C_N$, % carbon atoms present in ring structure.

A further important structural quantity is Φ, the degree of branching of the mixture, which is especially of interest in the study of isomerization phenomena[4]; for the investigation of aromatic fractions it is sometimes useful in distinguishing different types of aromatic molecules, e.g. monoaromatic rings, diaromatic rings, etc.[5]

For the direct quantitative estimation of the structural elements of mineral oil fractions, use can be made of the so-called "direct method", which is based on a quantitative analytical hydrogenation of the fraction to be investigated and accurate ultimate analyses and molecular weight determinations of both the original and the hydrogenated samples. This method, which has been described in detail in the literature,[6] allows the unambiguous determination of $\%C_A$ and R_T; to calculate R_A from $\%C_A$ and $\%C_R$ from R_T an assumption has to be made concerning the type of the rings and their manner of fusion; normally it is assumed that the rings, when present, are *six-membered* and *kata-condensed*, which assumptions seem to be justified by practical experience.

The direct method is very laborious and time-consuming. It can only be executed by highly skilled analysts. Since it is the only unambiguous and independent method for the analysis of crude oil fractions, it should always be employed in cases of doubt. Actually all reliable empirical methods, which have been developed for the investigation of mineral oil fractions and which are based on empirical relations of distinct physical properties, have been checked by the absolute *direct method*.

Waterman ring analysis.—This method can be considered to be the first reliable one for the analysis of mineral oil fractions and it is based on the empirical fact that for saturated hydrocarbons or hydrocarbon mixtures, there exists a linear relationship between hydrogen content and specific refraction, r^{20}_{spec}:

$$r^{20}_{spec} = \frac{n^2-1}{n^2+2} \cdot 1/d = 0.2013 + 0.00890\ \%H$$

in which n = refractive index (n_D^{20}), d = density (d_4^{20}), and %H = hydrogen content.

This relationship made it possible the analysis of *saturated* mineral oil fractions to replace the difficult and laborious ultimate analysis by a simple estimation of refractive index and density and to estimate R_N *graphically* by means of a simple *ring-analysis diagram*[7]. For the analysis of *aromatic* samples Vlugter *et al.* developed a method[8] based on data of specific refraction, molecular weight and aniline point; later on Leendertse[9] succeeded in developing a graphical method in which only *three* physical constants: refractive index, density, and molecular weight were sufficient to determine $\%C_A$, $\%C_R$, $\%C_N$, and the corresponding ring numbers.

Leendertse's method was worked out mathematically by Tadema, who correlated data of a large number of crude oil fractions of different origin and gave a final form to the ring analysis method in the formulas of the *n-d-M*-method[6,9] which nowadays have found general acceptance in the petroleum industry.

Later investigations demonstrated the applicability of viscosity data for the analysis of mineral oil fractions. The *ν-n-d* method and the *viscosity-nomogram method*[11] are based on kinematic viscosity, refractive index, and density and allow also the approximate estimation of the molecular weight from the physical constants mentioned.

For the estimation of the *degree of branching* ϕ (the average number of branchings per molecule) of saturated mineral oil fractions, Waterman and Leendertse[12] developed an empirical graphical method, based on data of the specific refraction and the specific parachor $p^{20}{}_{\text{spec}}$:

$$p^{20}{}_{\text{spec}} = \frac{\gamma\sqrt{\gamma}}{d}$$

The diagram of Waterman and Leendertse was improved and revised in later publications[4,13]. For the estimation of Φ in aromatic fractions a more general diagram has been developed recently[14], based on formulas of De Booijs[15]. It should be emphasized, however, that the various methods of branching analysis have only a qualitative, or at best semi-quantitative meaning. Because reliable absolute methods for branching analysis of hydrocarbon mixtures fail, the estimation of the degree of branching by the existing empirical methods is of some value only in comparative studies, but lacks any absolute significance.

Correlations of Physical Constants of Mineral Oils

As has been shown in the preceding paragraph, in principle three different physical constants are necessary for the ring-type analysis of mineral oil fractions, e.g. n, d, and M or ν, n, and d etc.

As a matter of fact, it can be expected that it must be possible to predict distinct physical properties of mineral oil fractions from properly chosen other physical constants. In the Delft Technological University extensive research has been carried out to confirm this and to develop practical and useful correlations which allow the mutual prediction of important physical data e.g.,

(*a*) Prediction of (*a*) average molecular weight from kinematic viscosity, refractive index, and, density[10]; (*b*) Prediction of surface of tension σ from kinematic viscosity and density[16]; (*c*) Prediction of ultrasonic sound velocity U from kinematic viscosity, density, and refractive index[17]; (*d*) kinematic viscosity of mineral oil fractions at an arbitrary temperature (70°) from the kinematic viscosity at 20°, the refractive index and the density[18]; and the simple relationship[19] (*e*) between ultrasonic sound velocity and surface tension of mineral oil fractions:

$$\sigma = 0.0354\,\eta - 20.6$$

In the next paragraph the application of these relationships has been demonstrated and compared against experimental on the data of a number of Kuweit crude oil fractions, in the next section.

Experimental Procedures

Distillation.—A preliminary distillation showed that the crude to be investigated did not contain products boiling in the gasoline range.

Small amounts of water, present in the crude, were removed by treatment with anhydrous sodium sulphate and occasional stirring.

The dried crude oil was distilled in a vacuum equipment at approx. 1 mm. Hg; ten fractions were collected at increasing distillation temperatures. The distillation residue (59% of the crude) was submitted to molecular distillation in a falling film apparatus[20]; in this way two more distillation fractions were obtained. The final residue (30·5% of the original crude), which was collected as a tarry mass, was not further investigated. Some data of the obtained fractions are recorded in Table I.

TABLE I

Distillation of Kuweit crude oil.

Fraction.	Wt. %of crude.	Boiling range.	Av. M.W.	%S.	Colour.	Consistency.
1	4.2	65—108°/5mm	187	0.16	Colorless	Liquid
2	3.5	108— 30°/5	199	0.32	,,	,,
3	4.4	130— 48°/5	222	0.47	Slightly yellow	,,
4	3.9	148— 58°/5	237	0.60	,,	,,
5	4.2	158— 68°/5	251	0.84	Yellow	,,
6	4.0	163— 74°/1	270	1.12	Brown-yellow	,,
7	4.0	174— 84°/1	289	1.20	Brown	,,
8	4.2	184— 92°/1	295	1.22	,,	,,
9	4.3	192—200°/1	334	1.21	,,	Pasty
10	4.5	200—205°/1	337	1.26	,,	Semi-solid
11	18.0	Molecular distillation	467	1.53	Dark brown	,,
12	10.3	Do	622	1.76	,,	,,
Residue	30.5	..	..	2.82	Nearly black	Tarry

Hydrogenation.—The fractions 1-10 were hydrogenated quantitatively in rotating autoclaves using nickel on kieselguhr as a catalyst at 300° as a maximum and a hydrogen pressure of 150-300 atmospheres. This analytical hydrogenation aims at a complete saturation of the oil fractions and simultaneous removal of foreign elements (sulphur) without further drastic structural changes of the oil molecules; thus a comparative study of the original fractions and their hydrogenation products, in which the aromatic rings have been transformed quantitatively into the corresponding naphthenes, becomes possible.

Table II records a review of the physical data, which were determined of the different fractions and their hydrogenation products in view of the application of different methods for the determination of their chemical structure.

TABLE II

TABLE II

Physical constants of Kuweit crude oil fractions and their hydrogenation products.

Fraction.	n^{20}_D.	d^{20}_4.	Av. M.W.	%S.	Kinematic viscosity (centistokes) $\log_{20}$.	$\log_{40}$.	$\log_{70}$.	$\log_{100}$.	Surface tension (dyne/cm) 20°.	Ultrasonic sound velocity (m/sec.,) 20°.	r^{20}spec.	p^{20}spec.
1	1.4799	0.859	187	0.16	0.485	0.314	0.116	—	25.4	1328	0.3307	2.613
1 hydr.	1.4550	0.828	—	—	0.458	—	—	—	27.9	1356	0.3277	2.776
2	1.4879	0.873	199	0.32	0.663	0.444	0.222	—	27.5	1403	0.3300	2.623
2 hydr.	1.4600	0.840	—	—	0.630	—	—	—	28.8	1380	0.3261	2.758
3	1.4898	0.877	222	0.47	0.806	0.576	0.322	—	28.6	1414	0.3295	2.637
3 hydr.	1.4620	0.843	—	—	0.774	—	—	—	29.0	1385	0.3261	2.753
4	1.4905	0.880	237	0.69	0.978	0.713	0.424	—	29.9	1423	0.3288	2.657
4 hydr.	1.4638	0.841	—	—	0.828	—	—	—	28.7	1389	0.3280	2.752
5	1.4978	0.892	251	0.84	1.176	0.863	0.535	—	30.5	1438	0.3285	2.635
5 hydr.	1.4679	0.853	—	—	1.020	—	—	—	29.5	1410	0.3258	2.732
6	1.5066	0.908	270	1.12	1.319	0.974	0.587	—	30.9	1453	0.3275	2.597
6 hydr.	1.4773	0.864	—	—	1.031	—	—	—	30.1	1418	0.3272	2.711
7	1.5099	0.912	289	1.20	1.667	1.247	0.819	—	31.5	1469	0.3279	2.598
7 hydr.	1.4756	0.871	—	—	1.469	—	—	—	30.5	1444	0.3236	2.698
8	1.5120	0.916	295	1.22	1.777	1.345	0.886	—	31.7	1475	0.3276	2.590
8 hydr.	1.4760	0.870	—	—	1.454	—	—	—	30.5	1441	0.3242	2.701
9	1.5164	0.924	334	1.21	1.99**	1.507	1.004	0.670	—	—		
9 hydr.	1.4802	0.880	—	—	1.73**	1.333	0.887	0.593	—	—		
10	1.5211	0.931	337	1.26	2.16**	1.628	1.088	0.736	—	—		
10 hydr.	1.4823	0.885	—	—	1.84**	1.396	0.939	0.640	—	—		
11	1.5192*	0.926*	467	1.53	—	—	—	—	—	—		
11 hydr.	—	—	—	—	—	—	—	—	—	—		
12	1.5332*	0.952*	622	1.76	—	—	—	—	—	—		
12 hydr.	—	—	—	—	—	—	—	—	—	—		

* 70°C

** Extrapolated

TABLE III

Chemical constitution of original and hydrogenated Kuweit crude oil fractions.

Fraction.	$n-d-M$ method							$\nu-n-d$ method							M.W.	Θ (general diagram)[14]
	$\%C_A$.	$\%C_N$.	$\%C_R$.	$\%C_P$.	R_A.	R_N.	R_T.	$\%C_A$.	$\%C_N$.	$\%C_R$.	$\%C_P$.	R_A.	R_N.	R_T.		
1	21	34	55	45	0.5	0.9	1.4	21	29	50	50	0.5	0.7	1.2	190	4
1 hydr.	1	55	56	44	0.0	1.4	1.4	2	54	56	44	0.0	1.3	1.3	190	2
2	23	33	56	44	0.6	0.9	1.5	26	29	55	45	0.6	0.9	1.5	205	2
2 hydr	1	54	55	45	0.0	1.5	1.5	1	53	54	47	0.0	1.5	1.5	205	2
3	21	30	51	49	0.6	1.0	1.6	23	31	54	46	0.6	1.0	1.6	215	3
3 hydr.	0	50	50	50	0.0	1.5	1.5	0	52	52	48	0.0	1.5	1.5	220	2
4	20	29	49	51	0.6	1.0	1.6	21	31	52	48	0.6	1.0	1.6	235	2
4 hydr.	3	40	43	57	0.1	1.3	1.4	3	42	45	55	0.1	1.3	1.4	235	2
5	22	28	50	50	0.7	1.1	1.8	21	32	53	47	0.6	1.2	1.8	245	2
5 hydr.	1	47	48	52	0.0	1.7	1.7	1	48	49	51	0.0	1.6	1.6	250	2
6	23	29	52	48	0.8	1.2	2.0	25	29	54	46	0.8	1.2	2.0	255	3
6 hydr.	9	37	46	54	0.3	1.4	1.7	7	46	53	47	0.2	1.5	1.7	240	2
7	24	25	49	51	0.9	1.1	2.0	25	25	50	50	0.8	1.3	2.1	290	3
7 hydr.	0	50	50	50	0.0	2.1	2.1	1	51	50	50	0.0	2.1	2.1	290	3
8	24	26	50	50	0.9	1.2	2.1	26	24	50	50	0.9	1.3	2.2	300	3
8 jhydr.	1	48	49	51	0.0	2.1	2.1	1	47	48	52	0.0	2.1	2.1	295	3
9	24	25	49	51	1.0	1.4	2.4	26	24	50	50	1.0	1.4	2.4	320	—
9 hydr.	0	49	49	51	0.0	2.5	2.5	1	51	50	50	0.0	2.4	2.4	320	—
10	26	24	50	50	1.1	1.3	2.4	28	24	52	48	1.1	1.5	2.6	325	—
10 hydr.	0	51	51	49	0.0	2.6	2.6	1	53	52	48	0.0	2.6	2.6	325	—
11	26	19	45	55	1.6	1.6	3.2	—	—	—	—	—	—	—	—	—
12	28	18	46	54	2.2	2.4	4.6	—	—	—	—	—	—	—	—	—

Structural Analysis.—Structural analysis of the oil fractions was performed by two different methods, namely the *n-d-M*[9] and *ν-n-d* method[10]; the latter also allowed the approximate estimation of the molecular weight.

To estimate the average number of branchings per molecule, ϕ, the general diagram[14] has been applied. The results of the analyses have been collected in Table III.

Correlations of Physical Constants.—In Table IV the results of some experimental and predicted physical properties of the Kuweit oil fractions are summarized.

TABLE IV

Comparison of experimental physical data of Kuweit oil fractions with data predicted from other physical constants.

	Molecular weight.		Surface tension (dyne/cm) at 20°.		Log. kinem. visc. at 70° (centistokes).		Ultrasonic sound velocity (m/sec.).		Surface tension (dyne/cm) at 20°.	
Fraction.	Exp.	*Predicted[10].	Exp.	*Predicted[16].	Exp.	*Predicted[18].	Exp.	*Predicted[17].	Exp.	**Predicted[19].
1	187	190	25.4	28.3	0.12	0.12	1382	1375	25.4	28.4
1 h	—	190	27.9	27.5	—	—	1356	1342	27.9	27.4
2	199	205	27.5	29.2	0.22	0.22	1403	1398	27.5	29.6
2h	—	205	28.8	28.2	—	—	1380	1363	28.8	28.3
3	222	215	28.6	29.6	0.32	0.32	1414	1410	28.6	29.5
3h	—	220	29.0	28.6	—	—	1385	1376	29.0	28.5
4	237	235	29.9	29.9	0.42	0.42	1423	1421	29.9	29.8
4h	—	235	28.7	28.7	—	—	1389	1381	28.7	28.6
5	251	245	30.5	30.5	0.54	0.54	1438	1437	30.5	30.2
5h	—	250	29.5	29.3	—	—	1410	1400	29.5	29.4
6	270	255	30.9	31.1	0.59	0.61	1453	1450	30.9	30.9
6h	—	240	30.1	29.7	—	—	1418	1409	30.1	29.6
7	299	290	31.5	31.2	0.82	0.82	1469	1464	31.5	31.4
7 h	—	290	30.5	30.3	—	—	1444	1428	30.5	30.6
8	295	300	31.7	31.5	0.87	0.87	1475	1470	31.7	31.7
8 h	—	295	30.5	30.3	—	—	1441	1440	30.5	30.4
9	334	320	—	—	1.00	1.01	—	—	—	—
9h	—	320	—	—	0.89	0.85	—	—	—	—
10	337	325	—	—	1.09	1.11	—	—	—	—
10 h	—	325	—	—	0.94	0.90	—	—	—	—

*From $\log\nu_{20}$, n_D^{20}, d_4^{20}.
†From $\log\nu^{20}$ and $d^{20}{}_4$.
**From ultrasonic sound velocity.

As follows from Table I, the Kuweit crude oil under investigation did not contain lower boiling fractions. Approximately 40% of weight of the crude could be distilled in vacuum (boiling point $<205°$ at 1 mm Hg), another 20% of weight of the crude was distilled molecularly. The sulphur content of the crude was relatively high (1.60% S); in the distillation fractions the weight% sulphur gradually increased from 0.16% in the lowest boiling fraction to 2.82% in the distillation residue.

The composition of the different oil fractions, as determined by the *n-d-M* method and the *ν-n-d*-method, show a remarkable constancy. Approximately 50% of carbon atoms are

present in paraffinic chains, approximately 25% in naphthenic rings and approximately 25% in aromatic rings and these figures show slight differences at increasing molecular weight of the fractions (compare Table III).

The results of the *n-d-M* and the *v-n-d* methods for the structural analysis of the oil fractions agree reasonably well. The data of the hydrogenated fractions show that hydrogenation is not complete in the case of the fractions 4 and 6.

The average number of branchings in the fractions is very small, even in the higher boiling fractions Φ does not exceed 3 per molecule. It should, however, be stressed that the determination of branchings, particularly in original oil fractions, has only a semi-quantitative character.

As follows from Table IV, several physical properties of the oil fractions, such as the average molecular weight, the surface tension, the ultrasonic sound velocity, and the kinematic viscosity at arbitrary temperatures, can be predicted with a reasonable accuracy from data of the kinematic viscosity at 20°, the refractive index (n_D^{20}) and the density (d_4^{20}). It should be remarked that several diagrams which are applied to predict the physical properties mentioned, have only been developed for straight-run fractions and may show small deviations when applied for saturated (hydrogenated) fractions. Besides, the surface tension is highly influenced by the presence of small amounts of surface-active impurities; this might explain the differences between the experimental values of the surface tension and the values predicted from kinematic viscosity and density on one hand, and from ultrasonic sound velocity on the other; it is at least remarkable that the values of the surface tension, predicted by both these completely independent methods, show such a close agreement (compare Table IV).

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Chemistry of Leucoanthocyanidins

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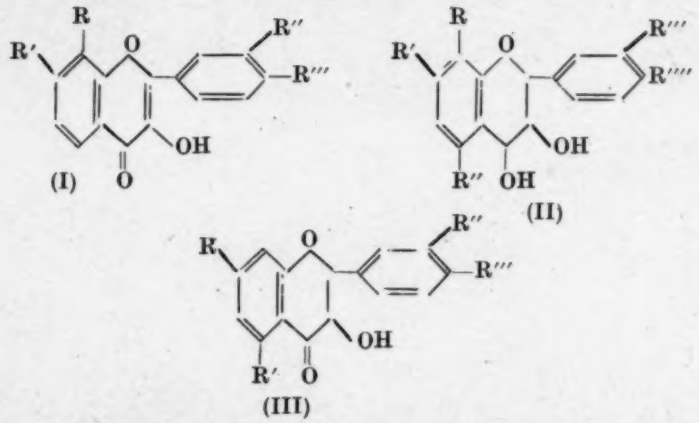
The leucoanthocyanidins are colorless, natural phenolic substances, which yield anthocyanidins on treatment with hot concentrated acids. The production of red colours from colourless material present in certain flowers, fruits, and leaves on treatment with strong acid has long been known. Their presence was reported in the leaves of the summer lime[1], in white grapes[2], and apples[3]. Robinson and Robinson[4] after a survey of the distribution of these compounds have shown that leucoanthocyanidins are widely distributed in plant kingdom, particularly in tannin-bearing plants and that majority of them (84%) yield cyanidin, and the rest, with a few exceptions, yield delphinidin. Paper chromatography of some commercial tannin extracts[5] has shown that a series of leucoanthocyanidins of increasing molecular weight in the range 300-1500 is usually present and that those of lowest molecular weight are most mobile when the chromatogram is developed with 2% acetic acid. These mobile compounds are monomeric leucoanthocyanidins and are identical with hydroxylated flavan-3,4-diols (II); some of them have been isolated in pure form[6].

In recent years there has been a growing tendency to regard leucoanthocyanidins as the possible precursors of 'Condensed tannins'. They can condense much more rapidly than the catechins. Their dimerization may occur between the 4-hydroxyl of one unit with C(6) or C(8) hydrogen of the other unit. In nature they are probably formed in the leaves and then move with carbohydrates and other materials down into the sapwood and heartwood, where they ultimately change into tannins and phlobaphene in course of time.

Because of their increased importance in the study of natural flavanoids, several methods have been developed in recent years to synthesise flavan-diols, especially flavan-3,4-diols[7]. Some of these methods are stereospecific, whereas others yield a mixture of racemates. Thus King and Clark-Lewis[6b] synthesised (±)-7, 8, 3′,4′-tetramethoxyflavan-3,4-diol (II : R″=H, R=R′=R‴=R⁗=OMe) (2e, 3a, 4e′) by the catalytic hydrogenation of the corresponding flavonol (I: R′=R″=R‴=OMe). Hydrogenation of dihydroflavonol (III) has given varied results. Kulkarni and Joshi[7a] have reported the formation of a *cis*-4′-methoxy-6-methylflavan-3, 4-diol (2e,3e, 4a′) by the hydrogenation of 4′-methoxy-6-methyldihydroflavonol in acidic medium, though Bognar and Rakosi[7b] obtained by the hydrogenation of dihydroflavonol in acidic medium a flavan-3,4-diol, which was identical with the flavan-3-, 4-diol that they obtained by metal hydride reduction of dihydroflavonol. The latter diol is a mixture of racemates as has recently been shown by the same authors[7c]. Reduction of dihydroflavonols by metal hydrides generally gives a mixture of recemates, some of which have been separated either by their fractional crystallisation[6a] or by the column chromatography of their acetates[7a]. A new stereospecific method for the diol synthesis proceeds *via* the 4-amino compound of the dihydroflavonol, which has been shown to yield exclusively the 4- α-epimer[7c]. Another stereospecific synthesis consists in the introduction of an acetoxyl group of the C(4) of a 3-hydroxyflavan by lead tetra-acetate followed by hydrolysis[8]. The yield in the last method, however, drops considerably as the flavan nuclei are increasingly substituted by the methoxyl groups. The causes for side-reactions in these cases have been explored by these authors and they have established that in a highly methoxylated flavanoid molecule C(2) and the highly anionoid

nuclear carbon atoms provide alternate site for acetoxylation. It has also been shown that the 4(OH) groups introduced by lead tetra-acetate take up quasi-equatorial conformation. Thus from (+)-catechin tetramethyl ether they obtained (+)-leucocyanidin tetramethyl ether (II: R=H, R′=R″=R‴=R⁗=OMe), which was found identical with the (+)-leucocyanidin tetramethyl ether, obtained from (+)-taxifolin tetramethyl ether either by partial hydrogenation in neutral medium or by its reduction with a mixture of lithium aluminium hydride and aluminium chloride[6i,9-12]. The latter diol formed an isopropylidene derivative, indicating it to be a *cis*-diol having a (2a, 3a, 4e′) conformation. This conversion of a catechin into a leucoanthocyanidin provides a missing link in the flavanoid interconversions.



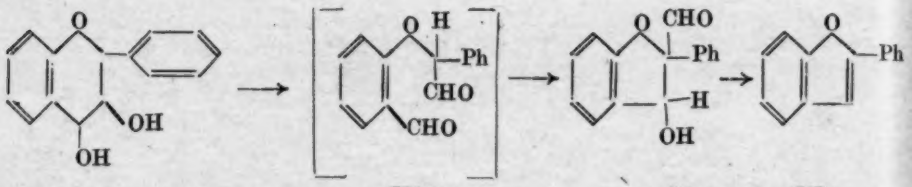
Bokadia and Brown[13] have prepared 4′-methoxyflavan-3,4-diol (II:R ⁗=OMe, R=R′=R″=R‴=H)by different methods and they have shown that reduction of 4′-methoxydihydroflavonol (III : R‴=OMe, R=R′=R″=H) by metallic hydrides or its hydrogenation in acidic medium gives the same racemate of the diol. Reduction with a mixture of lithium aluminium hydride and aluminium chloride, however, gives a different racemate. The stereochemistry of these diols is under investigation.

The recent investigations of Birch and his collaborators[14], Hardegger *et al.*[15], and Bokadia, Brown, and Sommerfield[16] give a composite picture of the relative and absolute configuration of catechins. Hence the relative and absolute configurations of the leucoanthocyanidins can be deduced from a combination of configuration of the corresponding catechins obtained by their hydrogenolysis[10,17] and the configuration of the diol. The *cis* nature of the diol can be inferred by the formation of cyclic derivatives like carbonate or isopropylidene. The conformations of these compounds can also be established by synthesising them in the racemic form by employing stereospecific reactions. Thus King and Clark-Lewis[6b] have successfully assigned a (2e, 3a, 4e′) conformation to melacacin by its sythesis from the corresponding flavonol and from the *cis* nature of the diol. The recent observation of Bognar *et al.*[7c] that a di-equatorial *trans* diol (3e, 4e′) could also form cyclic derivatives, however, invalidates this method for differentiating a *cis* diol from a di-equatorial *trans* diol. A more promising method of differentiation between the different diols would be to find the rate of cleavage of these diols by reagents like lead tetra-acetate or periodate.

An important feature of the chemistry of leucoanthocyanidins is that the anthocyanidins produced from them have lost the 4-hydroxyl group and retained the 3-hydroxyl

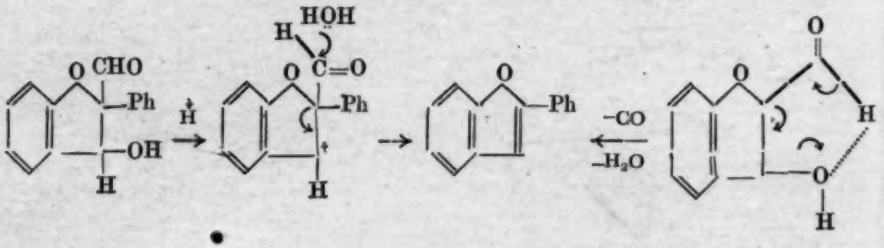
group. Baur, Birch, and Hillis[18] pointed out that the first stage of transformation of a leucoanthocyanidin to anthocyanidin was the formation of a 3-ketoflavan by acid-catalysed dehydration. Flavan-3-ones like flavan-3, 4-diols are in the same state of oxidation as dihydroanthocyanidins so that flavylium salts must be produced by oxidation. Overall mechanistic possibilities are direct oxidation and disproportionation. The low yield of anthocyanidins from leucoanthocyanidins is due to a competing reaction leading to condensed tannins. This is explicable if flavan-3-ones are intermediates, for they would be very unstable and their polymerization could occur by aldol type of condensations of the ketone group with the phloroglucinol nucleus[19-20].

Bokadia, Brown, and Cummings[8] have investigated in detail the cleavage of flavan-3,4-diols by lead tetra-acetate. This fission product in the case of simple flavan-3, 4-diol (II: R=R′=R″=R‴=R⁗=H) was proved to be 2-phenyl-2-formyl-3-hydroxy-2, 3-dihydrobenzofuran (V). Treatment of this dihydrobenzofuran with dilute sulphuric acid or its sublimation afforded 2-phenylbenzofuran[21] (VI). The entire sequence could be represented as follows:



(IV) (V) (VI)

In the acidic medium the dialdehyde (IV), the initial cleavage product, undergoes an acid-catalysed intramolecular aldol-condensation to form the hydroxyaldehyde (V), which changes into 2-phenylbenzofuran by the following ionic mechanism:

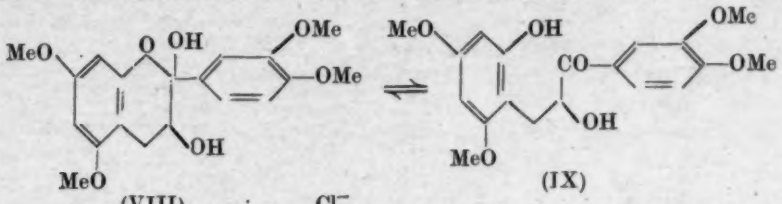


(VI) (VII)

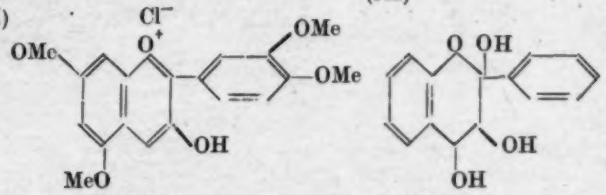
The steric squeezing out effect of the bulky phenyl group may also help the elimination at C(2). In case of pyrolysis the conversion may involve a cyclic transition state (VII).

The above conversion is significant in view of the recent findings of Gramshaw *et al.*[22], who have shown that flavan-2,3-diols may also be regarded as another type of leucoanthocyanidins, since these also yield anthocyanidins on treatment with acid. Thus 3′, 4′, 5, 7-tetramethoxyflavan-2,3-diol (VIII), which mostly exists as dihydro-α-2-dihydroxy-4,6,3′,4′-tetramethoxychalkone (IX), yields cyanidin chloride tetramethyl ether (X) on treatment with acid. These findings also validate the original formulation of Robinson

and Robinson[4] of leucoanthocyanidins as flavan-2, 3, 4-triols (XI). Hence a method to differentiate among flavan-2, 3-diols, flavan-3, 4-diols, and flavan-2, 3, 4-triols would be

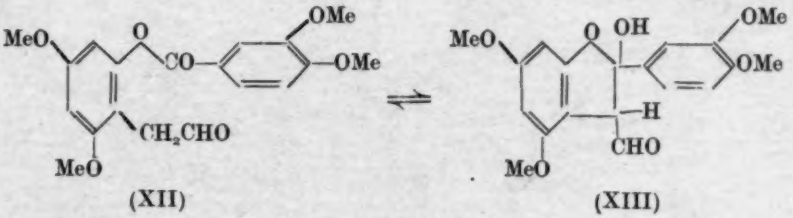


(VIII) (IX)

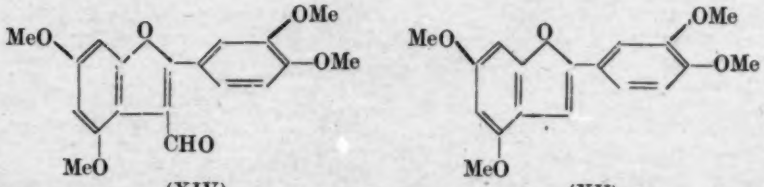


(X) (XI)

of great practical importance in the study of leucoanthocyanidins. The periodate fission of 3′,4′,5,7-tetramethoxyflavan-2,3-diol afforded a mixture of veratric acid and an aldehyde-ester (XII). Although the ester might be capable of intramolecular condensation, this has not been reported[22]. Even if condensation occurred, the resuting dihydrobenzofuran (XIII) would be expected to undergo dehydration to form 2-aryl-3-formylbenzofuran (XIV) rather than elimination of formic acid to form 2-arylbenzofuran (XV)



(XII) (XIII)

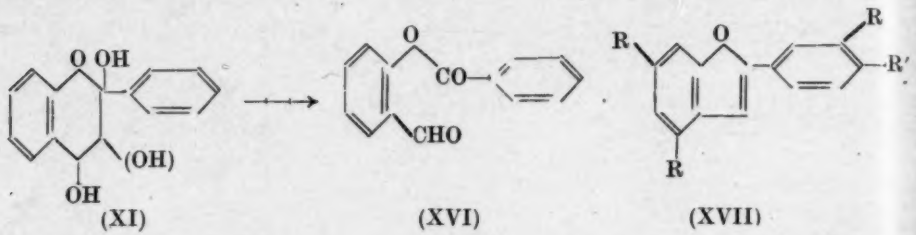


(XIV) (XV)

A flavan-2, 3, 4-triol (XI) would yield on oxidation an aldehyde-ester (XVI) which is incapable of any intramolecular condensation. From the evidence cited above it follows that the conversion of a flavan-3, 4-diol into a 2-arylbenzofuran can be used to differentiate it from 2, 3-diols and 2,3,4-triols.

To test the general applicability of the method, it was applied to 4′-methoxyflavan-3,4-diol. The conversion occurred in a very good overall yield to furnish 2-*p*-methoxyphenyl-

benzofuran (XVII : R=H, R′=OMe). When this method was applied to 3′, 4′, 5, 7-tetramethoxyflavan-3,4-diol, the results were, however, rather disappointing with acetic acid as a solvent. Replacement of acetic acid by bezene yielded a product, which on acid treatment afforded a 5% yield of 4, 6-dimethoxy-2-(3′, 4′-dimethoxyphenyl)-benzofuran (XVII: R=R′=OMe).



(XI) (XVI) (XVII)

This conversion can also be used in finding the positions of the hydroxyl groups in the two benzene nuclei provided that the corresponding reference compounds, viz. 2-arylbenzofurans, are known and it provides a new method for flavanoid ring contraction.

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Studies on Synthesis of Compounds Designed as CNS Depressants

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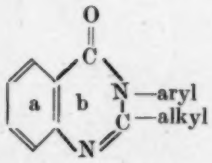
Drugs which depress the Central Nervous System (CNS) may affect the CNS generally or some specific centre within it. It is difficult to distinguish between the two modes of action. Also a drug may combine both types of action. Morphine-like analgesics and anti-convulsant drugs probably act on specific centres in the CNS. Hypnotics, narcotics, and general anaesthetics, on the other, depress the CNS generally. But it is seldom that a drug of this class has only a single activity and only a single mode of action. Analgesia, sedation, and hypnosis are probably only different stages of partial depression of the CNS. Drugs designed to be possibly active in one field turn out to have useful activity in an allied or even in a difierent field. Thus Dolantin (Pethidine), now so widely used as an analgesic, was originally designed by Eisleb as an antispasmodic.

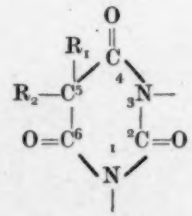
Over the last few years, we have been engaged in the synthesis of compounds likely to be active as CNS depressants. Our work lies mainly in the field of (*i*) synthesis of quinazoline derivatives, (*ii*) synthesis of tetrahydroquinoline derivatives, and (*iii*) synthesis of β-phenylethylamines and tetrahydroisoquinoline derivatives.

Derivatives of Quinazoline

Seventeen new 4(3-H) quinazolones of the general formula (I) were synthesised by Kacker and Zaheer[1] by the general method of Grimmel, Guenther, and Morgan[2], and were screened at the K. G. Medical College, Lucknow, and the results reported by Gujral *et al.*[3,4]



(I)



(II)

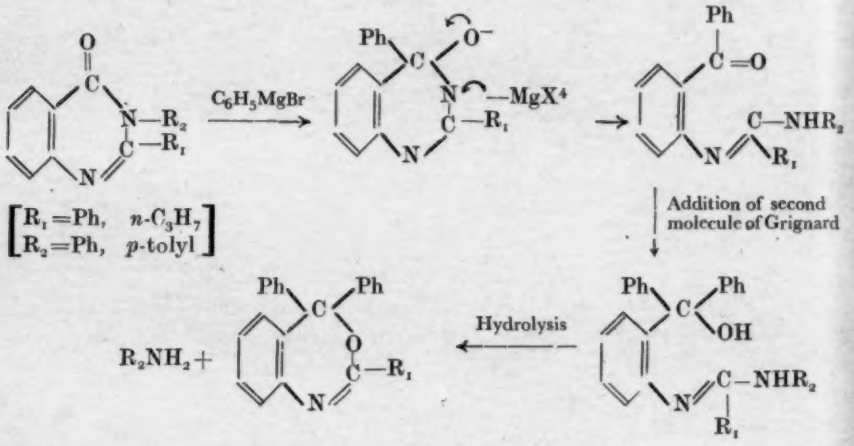
Although these compounds indicated no analgesic activity, they were found, however, to be potent hypnotics, the most potent and clinically useful compound being 2-methyl-3-*ortho*-tolyl-4(3H)-quinazolone. After animal trials, it was tested clinically on medical and surgical patients as well as on healthy volunteers and found to be a hypnotic of lesser toxicity and greater duration of activity than diallylbarbituric acid in comparable doses. This hypnotic activity in the quinazolones could possibly be explained by the presence of

the basic barbiturate skeleton in these compounds as can be seen by comparing structures (I) and (II). The ring in (I) could be considered analogous to C_4-alkyl chain at C_5 of (II).

This discovery of hypnotic activity for the first time in 4(3H)-quinazolones synthesised in this laboratory has led to a spate of work in this field at various laboratories abroad. A number of new quinazolones have now been synthesised and screened, but 2-methyl-3-*ortho*-tolyl-4(3H)-quinazolone still remains the most potent, with no adverse side effects. Ravina[5] has also described its pharmacological action. The compound is now marketed by Boots Pure Drug Co. Ltd., under the name Melsedin. Laboratories Toraude, Paris, have also obtained a British Patent for its preparation (B.P. 843,073).

Work at the Strasenburgh Laboratories[6] in U.S.A. has shown that this compound (named Tuazole by them) prolongs and potentiates the feeble analgesic activity of codeine. Gujral *et al.*[4] have also reported anticonvulsant activity in quinazolones. The B.D.H. laboratories are also pursuing this line of work[7].

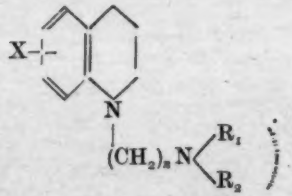
An aspect of chemical interest is the action of the Grignard reagents on these quinazolones. This was studied by us with four quinazolones[8] and found to lead to the fission of the heterocyclic ring with elimination of the arylamine and formation of benzoxazines. The reaction probably proceeds as follows:



[R_1=Ph, n-C_3H_7; R_2=Ph, p-tolyl]

Derivatives of Tetrahydroquinolines

Whereas several hundreds of compounds derived from quinoline have been synthesised and pharmacologically screened (mainly as antimalarials and amoebacides), derivatives of tetrahydroquinoline do not appear to have received the same attention. In our laboratory twenty-six new compounds of the general formula (III) have now been synthesised.[9]



(III)

X=alkyl, alkoxy or hydroxy
R_1=R_2=alkyl or heterocyclic residue
n=1–3

That such compounds have not so far received adequate attention may be due to the lack of convenient methods of preparing the desired tetrahydroquinolines in good yields. The tetrahydroquinolines are generally obtained by high pressure hydrogenation of the corresponding quinolines. The yields are not uniformly good and hydrogenation leads to a mixture of products of varying degree of hydrogenation. The methods that we have used for preparing the tetrahydroquinolines are:

(*i*) ***Lithium aluminium hydride reduction of appropriately substituted 3,4-dihydrocarbostyrils.***—The dihydrocarbostyrils can be prepared in good yields from *o*-nitrobenzaldehydes as described by us earlier[10].

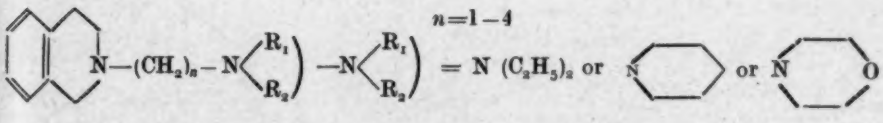
(*ii*) ***Reduction of the corresponding quinolines by nickel-aluminium alloy in alkali solution.***—The reduction proceeds smoothly in yields of 70% and over. This is an extension of a method first described by Papa *et al*[11]. The tetrahydroquinolines are then condensed with freshly prepared alkylaminoalkyl chlorides. The (*N*-alkylaminoalkyl)-1,2,3,4-tetrahydroquinolines, which were obtaind in good yields in this way, are now being evaluated for biological activity. One of these, in preliminary screening, has shown interesting antispasmodic and anticonvulsant activity. Its pharmacological action is in some respects reminiscent of the action of Reserpine[12].

Mayer and co-workers[13] have cyclised *m*-substituted *N*-(γ-chloropropionyl)anilines with aluminium chloride and obtained mixtures of 5- and 7-substituted dihydrocarbostyrils, but they could not assign structures to the individual compounds. We synthesised the 7-substituted isomers unequivocally from the corresponding *o*-nitrocinnamic esters during the course of the above work and thus were able to assign structures to Mayer's compounds also.[9]

Carbostyril provides a classical example of lactam-lactim tautomerism. 3,4-Dihydrocarbostyrils can, however, exist only in the lactam form. A comparison of the U.V. and I.R. spectra of the substituted carbostyrils and corresponding 3, 4-dihydrocarbostyrils, prepared by us, has shown that the carbostyrils also exist preponderantly in the lactam form[14], the carbonyl peak showing at 6.02 μ.

Isoquinoline Derivatives

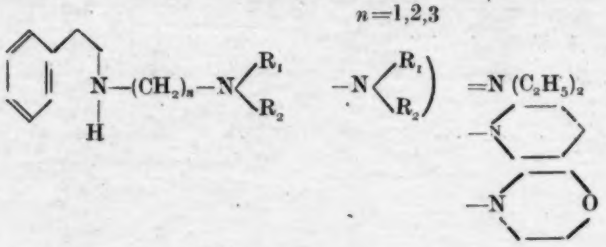
Morphine contains an octahydroisoquinoline system and several isoquinoline derivatives have been synthesised for testing as analgesics and antispasmodics—till recently with negative results. We have synthesised some (*N*-alkylaminoalkyl)-1,2,3,4-tetrahydroisoquinolines (IV):



(IV)

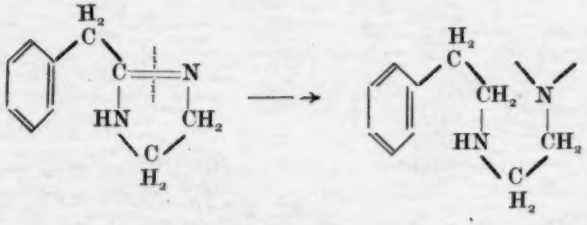
and are extending the synthesis to tetrahydroisoquinolines carrying alkyl, hydroxy, alkoxy and chlorine substituents in the benzene ring[15]. The compounds synthesised are being screened pharmacologically.

The tetrahydroisoquinolines needed for the above synthesis have been obtained by the Pictet-Spengler synthesis from appropriate β-phenylethylamines. β-Phenylethylamines themselves are well known to possess significant biological properties, generally sympathomimetic. We have prepared a number of β-phenylethylamines, some already known and some new, and have converted these also into dialkylaminoalkyl derivatives (V).



(V)

These compounds may be regarded as open-chain analogues of Priscooline (VI), a valuable vasodilator drug.



(VI)

Preliminary results of screening indicate spasmolytic activity in these compounds.

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Colorimetric Methods for the Determination of Osmium

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Osmium, a minor constituent in platinum metals, finds wide use in platinum jewellery, pen-point materials, in phonograph needles and as catalyst. The quantity of osmium in these materials being very small, it is usually estimated colorimetrically though some workers tried with strychnine[1-2], brucine[3], 2-phenylbenzothiazole[2], and thionalide[4] in its gravimetric determination.

For colorimetry, prior removal of osmium by distillation[5-8,4] is preferable to do away with the influences of other platinum metals. The organic reagents proposed till now are thiourea, *NN'*-di(2-tolyl)thiourea, 1,4-diphenylthiosemicarbazide, naphthylamine sulphonic acids and tetraphenylarsonium chloride. Of these, thiourea, which forms with osmium tetroxide or chloro-osmate a rose-red colour, was first employed by Tschugaeff[9] for detection of osmium and he found the reaction to be specific and sensitive to 0.1 p.p.m. of the element. The formula of the complex as suggested is $Os(NH_2\text{-}CS\text{-}NH_2)_6\text{-}Cl_3OH$. Sandell utilises the reagent for determination of traces of osmium, which in the tetravalent state obeys Beer's law from 1 to 3 p.p.m. Ayres and Wells[10] during a spectrophotometric study of the osmium-thiourea complex observe that the system, with a sharp transmittancy minimum at 480mμ and a less applicable band centering at about 540mμ, obeys Beer's law at 480 mμ with 1 to 100 p.p.m. of osmium. The optimum concentration range is from 8 to 40 p.p.m.,. where the percentage relative error per 1% absolute photometric error is 2.9. Of the platinum metals, only palladium and ruthenium interfere. The thiourea method has been found suitable by Allan and Beamish[11] for determination of the losses of osmium by fire assay and by Dwyer and Gibson[12] for osmium in organic compounds. The suggestions of Sauerbrunn and Sandell[13] that osmium tetroxide in its reaction with thiourea in acid medium is reduced to trivalent state to form $Os(NH_2\text{-}CS\text{-}NH_2)_6^{3+}$ is contrary to the earlier data where osmium has been claimed to be in the quadrivalent state. In another publication[14] these authors suggest the removal of osmium from ruthenium by oxidation with nitric acid to tetroxide and its subsequent extraction with chloroform. The colour developed on the addition of sulphuric acid solution of thiourea to the chloroform extract is then measured at 480mμ. The method is applicable to 5 to 1000 μg. of osmium. Chloride ion should be absent because through the formation of chloro-osmate it resists the oxidation of osmium to tetroxide.

Two other reagents, *NN'*-di(2-tolyl)thiourea and 1,4-diphenylthiosemicarbazide, have been introduced by Geilmann and Neeb[15] for the spectrophotometric determination

of osmium. Osmium (VI) complex formed by heating at 100° with *NN'*-di(2-tolyl)thiourea solution in 6*N* hydrochloric acid containing 5% stannous chloride is cooled and after extraction with chloroform its extinction is measured at 490mμ. The error is ±3%. Oxidising agents, sulphite, palladium, rhodium and ruthenium, iridium, and platinum interfere. 1,4-Diphenylthiosemicarbazide complex of osmium is usually extracted by chloroform and measured at 520 mμ.

With 1-naphthylamine-3,5,7-trisulphonic acid Wingfield and Yoe[16] find the hexavalent osmium at *p*H 1.5 to form a stable violet complex having absorption maximum at 560 mμ and the system obeys Beer's law up to 6.0.p.p.m. The coloured constituent contains osmium and the reagent in a ratio of 1:2. A large number of ions including platinum metals interfere in the determination. The method therefore requires preliminary separation of osmium tetroxide by distillation with nitric acid. In a similar investigation of Steele and Yoe[17] with a number of naphthylamine sulphonic acids, all the acid-osmium complexes have been found to have a fairly sharp peak at 560mμ and to adhere to Beer's law over an osmate concentration of 0.1 to 6 p.p.m., but a large number of ions interfere beyond 1:1 concentration.

Tetraphenylarsonium chloride[18] forms with a hexachloro-salt of osmium a yellow complex which is extractable by chloroform and its absorption of peak at 375 mμ is a suitable wave length for the study of the colour system as it obviates the interference of ions. Sulphite, perchlorate, and the ions, which are precipitated by the reagents, should be absent. Ruthenium up to 200-fold excess has no influence.

Recently Watanabe[19] has determined osmium in presence of ruthenium by measuring the colour of sodium osmate at 520 mμ. In this method a mixture of osmium and ruthenium is fused with sodium peroxide and sodium hydroxide and the aqueous extract is heated with ethanol at 30° to 40° for 15 minutes when ruthenium is precipitated and osmium remains in solution as sodium osmate. This is then determined in the supernatant solution.

A comparative account of these investigations is recorded in Table 1.

TABLE I

Organic colorimetric reagents for osmium.

Reagent	Oxidation state of osmium.	Acidity or *p*H.	Analytical wave length.	Cell thickness.	Conc. range (p.p.m.)	References.
Thiourea	Octa-, tetra-	4*N*-HCl 6 to 9*N*	480 mμ	1 cm.	8 to 40	6, 10-14
NN'-Di (2-tolyl)-thiourea	Tetra-	HCl	490	2	15 to 175	15
1,4-Diphenyl-thiosemi-carbazide	Do	0.05*N*	520	2	7 to 60	15
Naphthylamine sulphonic acids	Hexa-	*p*H 1.5	560	1	1.5 to 5.5	16,17
Tetraphenyl-arsonium chloride	Do	0.2 to 0.3*N* -HCl	375	2	0.3 to 1.5	18

Among the existing colorimetric methods discussed, those due to thiourea have found wide application. The unstable character of the complex and the low sensitivity of the reaction require higher concentrations of the reagent and acid. The colour reaction of naphthylamine sulphonic acid, which is believed to be due to the presence of amino group in the molecule takes long period for full colour development; it is restricted only to hexavalent osmium, which has been suggested to form a 1:2 complex with the reagent.

To examine whether the amino groups actually form a co-ordination complex with osmium and thereby develop a colour and whether organic molecules with such groups can be used as spectrophotometric reagents, systematic investigations with regard to the analytical behaviour of the aromatic amines, amino-acids, aminophenols, and aminonaphthols towards osmium, in different valence states, have been undertaken by us. These include studies on the region of maximum absorption of the colour complexes, the validity of Beer's law, optimum range with percentage relative error, the effects of *p*H, reagent, time, and foreign ions on the colour system, and the composition and dissociation constant of the complexes formed in solution. The aminophenols and aminonaphthols with suitably situated amino and hydroxyl groups behave as strong co-ordinating ligands and, moreover, these usually act as reducing agents in photography[20] for the reduction of gold compounds to metallic gold[21] and of phosphomolybdate to molybdenum blue[22-25]. The amino-acids, such as anthranilic acid, are known to form inner-metallic or co-ordination complexes with a number of bivalent metals.

In what follows are given the findings on the use of anthranilic acid[31], *m*-aminobenzoic acid[32], sulphanilic acid[33], *o*-aminophenol *p*-sulphonic acid[34], 1-amino-2-naphthol-4-sulphonic acid[32] and 1-amino-8-naphthol-3, 6-disulphonic acid[34] as spectrophotometric reagents for osmium.

At the very outset it is better to point out that for studying the reaction of octavalent and tetravalent osmium with the above reagents, use has been made of pure osmium tetroxide (OsO_4) and potassium chloro-osmate (K_2OsCl_6). But since pure salt of hexavalent osmium could not be procured, it was prepared by reduction of an alkaline osmium tetroxide solution with alcohol. Reactions of osmium in different valence states with any of the reagents mentioned above lead to formation of the same complex as is evident from their identical colour reaction, same region of absorption maximum and similar tolerance to *p*H variation. But as osmium (VI) solution contains some alcohol, which causes partial bleaching of the colour, the optical density of the colour complex formed by it is always less than that of the complex formed by an equal amount of osmium (VIII) or osmium (IV). Hence the comparative data with regard to sensitivity of the reaction, adherence to Beer's law, optimum concentration range, and prcentage relative error, as obtained with osmium (VIII) only, are given, though all such observations with osmium (VI) have been made.

Anthranilic acid[31] and sulphanilic acid[33] form stable dark violet colour complexes with osmium but *m*-aminobenzoic acid[32] exhibits a purple colour. These three complexes show maximum absorption at wave lengths of 460 mμ, 490 mμ and 500 mμ and at the *p*H ranges of 5.5 to 6.5, 1.8 to 3.5, and 4.5 to 6.0 respectively. Reactions of osmium with anthranilic acid and *m*-aminobenzoic acid take place in tetra-, hexa-, and octa-valent states, but with sulphanilic acid it is restricted only to hexa- and octa-valent states. With osmium (IV) the colour develops on heating in less than 10 minutes, but with osmium (VI) and

osmium (VIII) sufficiently stable colour with maximum intensity is obtained only on keeping in the cold for an hour or two. Heating should be avoided during reactions with osmium (VI) and osmium (VIII) as otherwise black osmium dioxide separates.

With the first and the second reagents osmium (VIII) obeys Beer's law from 0.5 to 8 p.p.m., whereas for the third reagent it is from 0.5 to 9 p.p.m.; but the optimum concentration ranges, as determined by the method of Ringbom[26], are respectively, 2 to 6 p.p.m., 3 to 8 p.p.m., and 2 to 8 p.p.m. where the percentage relative errors per 1% absolute photometric error, evaluated by Ayres equation[27], are 2.8, 2.8, and 3.02.

Composition studies by the continuous variation[28], molar ratio[29], and slope ratio[30] methods suggest that with osmium (IV) anthranilic acid forms a 1:1 complex. The first two methods also show that a 1:2 complex is formed between osmium (VI) and sulphanilic acid. The molar ratio method further reveals that osmium (VIII) or osmium (VI) oxidises a portion of anthranilic acid or *m*-aminobenzoic acid and is itself reduced to osmium (IV), which then reacts with the rest of the unoxidised reagent to form a 1:1 complex, the complex with the former reagent being very stable and that with the latter, unstable.

The dissociation constants of osmium (IV)–anthranilic acid and osmium (VI)–sulphanilic acid complexes are 4.6×10^{-5} and 1.2×10^{-7} respectively.

Aminophenol and aminonaphthol sulphonic acids develop a very strong coloration with octa- and hexavalent osmium in weak acid mediums, but have no action on its tetra-, tri- and bivalent states.

In both octa- and hexavalent states osmium forms in acid solutions dark brown (absorption maximum at 440 mμ) and brown (absorption maximum at 470-480 mμ) colour complexes with *o*-aminophenol-*p*-sulphonic acid, 1-amino-2-naphthol-4-sulphonic acid and 1-amino-8-naphthol-3,6-disulphonic acid respectively. The optimum *p*H ranges are 2.5 to 4, 4 to 5.5, and 4.5 to 6.0 respectively. With *o*-aminophenol-*p*-sulphonic acid and 1-amino-8-naphthol-3, 6-disulphonic acid Beer's law is obeyed with 1 to 10 p.p.m. of osmium (VIII) having optimum concentration range of 2 to 8 p.p. m. where percentage relative errors per 1% absolute photometric error are 2.98 and 2.93 respectively. With 1-amino-2-naphthol-4-sulphonic acid, there is conformity to Beer's law from 1 to 14 p.p.m. of osmium with an optimum range of 3 to 10 p.p.m. The percentage relative error per 1% absolute photometric error for the said range is 2.82.

Composition studies of the three complexes in acid solutions indicate that osmium (VI) forms a 1:2 complex with each of these reagents. The dissociation constants of dark brown, brown, and brownish black complexes are 1.2×10^{-7}, 2.05×10^{-9}, and 1.2×10^{-9} respectively.

Application of the molar ratio method to the dark brown and brownish black complexes points to the fact that the reagent is first oxidised by osmium (VIII) and then the excess of the reagent forms a 1:2 complex with the reduced osmium (VI).

A comparative account of the ractions is shown in Table II.

TABLE II

Reagent.	Oxidation state of osmium.	*p*H.	Wave length for max. absorption.	Conc. range of osmium for adherence to Beer's law (p.p.m.).	Sensitivity (/cm^2)	Complex nature (Metal: reagent ratio).	Dissociation constant of the complex.
Anthranilic acid	Octa-, hexa- and tetra-	5.5 to 6.5	460 mμ	0.5 to 8 for Os (IV) or Os (VIII)	0.008 for Os (IV) or Os (VIII)	1 : 1 between Os (IV) and reagent	4.6×10^{-5}
m-Aminobenzoic acid	Do	4.5 to 6.0	500	0.5 to 8 for Os (VIII)	0.012 for Os(VIIII)	Probably 1:1 between Os (IV) and reagent	..
Sulphanilic acid	Octa- and hexa-	1.8 to 3.5	490	0.5 to 9 for Os (VIII)	0.01 for Os (VIII)	1:2 between Os (VI) and reagent	1.2×10^{-7}
o-Aminophenol-*p*-sulphonic acid	Do	2.5 to 4.0	440	1 to 10 for Os (VIII)	0.01 for Os (VIII)	1:2 between Os (VI) and reagent	1.2×10^{-7}
1-Amino-2-naphthol-4-sulphonic acid	Do	4.0 to 5.5	470-480	1 to 14 for Os (VIII)	0.014 for Os(VIII)	1:2 between Os(VI) and reagent	2.05×10^{-9}
1-Amino-8-naphthol-3, 6-disulphonic acid	Do	4.5 to 6.0	480	1 to 10 for Os (VIII)	0.011 for Os(VIII)	1:2 between Os(VI) and reagent	1.2×10^{-9}

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Formation of Benziminazoles from *o*-Phenylenediamines and Aromatic Aldehydes

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Benziminazoles may be prepared by a variety of methods which have been very well summarised in an exhaustive review by Wright[1] and in an excellent monograph by Hofmann[2]. In the present article, the formation of benziminazoles from *o*-phenylenediamines and aromatic aldehydes alone is reviewed.

Condensation of o-*Phenylenediamine with One Mole of Aromatic Aldehydes*

In acidic or alcoholic medium *o*-phenylenediamine condenses with one mole of an aromatic aldehyde resulting in the monoanil[3-8] (I). Depending on the reactivity of the aldehyde, there is a possibility of the formation of dinail (II), only half the diamine being consumed in the reaction[8]. When the condensation is carried out in an oxidising atmosphere, 2-substituted benziminazoles (III) are obtained. Alternately, the monoanils independently prepared may be subjected to oxidative cyclisation to yield the benziminazoles. A wide variety of oxidising agents[6,7,9-20] have been successfully applied for the preparation of benziminazoles by this method.

Condensation of o-*Phenylenedimaine with Two Moles of Aromatic Aldehydes*

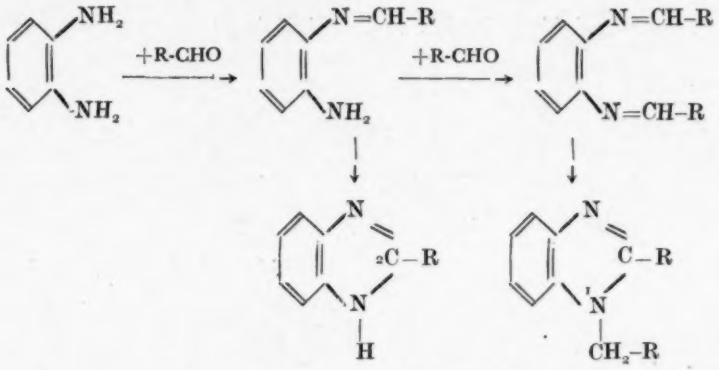
Dianils (II) are obtained in good yields by the condensation of the diamine with two moles of an aldehyde in alcoholic medium[3,4,8,21-24], whereas the reaction under acidic conditions leads to the formation of the isomeric 1,2-disubstituted benziminazoles (IV)[21,22,25-28].

The condensation of the diamine with a typical aromatic aldehyde has been studied to determine the optimum conditions for the formation of benziminazoles. The addition of reactants in glacial acetic acid at room temparature and working up the products after one hour was found to be the best method. The separation of mono- and disubstituted benziminazoles formed in the reaction could be effected by taking advantage of the fact that the former are preferentially soluble in dilute acetic acid. Several aromatic aldehydes carrying alkyl, alkoxy, hydroxy, halo, nitro, and amino groups were successfully condensed with-*o*-phenylenediamine following this method[29-31].

The condensation with aldehydes having hydroxy and amino substituents resulted in the exclusive formation of 1,2-disubstituted benziminazoles (IV) in nearly quantitative yields. Alkyl-, alkoxy-, halo-,and nitro-substituted aldehydes yielded in addition to the disubstituted benziminazoles, varying amounts of mono-substituted compounds (III). Moreover, dianils (II) have been isolated, even under the acidic conditions made use of

in the present experiments, with salicylaldehyde and 5-nitrosalicylaldehyde; these anils could be cyclised to the isomeric disubstituted benziminazoles by heating with acetic acid.

The formation of mono- and disubstituted benziminazoles from the diamine and two moles of aldehydes thus appears to proceed through the intermediate monoanils and dianils respectively, as indicated below. The oxidative cyclisation of the monoanils to the mono-substituted benziminazoles may be taking place by the action of air, as reported by earlier workers[3,4,32].



The key intermediate in the condensation seems to be the monoanil (I) which may either undergo oxidative cyclisation resulting in the mono-substituted benziminazole (III) or condense further with another mole of aldehyde, leading to the formation of the di-substituted benziminazole (IV) through the dianil (II). The course of the reaction appears to depend on the nature of the substituent in the aryl group of the monoanil. When the substituent is an electron-releasing group (OH, NMe_2), di-substituted compound is exclusively formed, whereas electron-attracting groups (NO_2,Cl) give rise to mono-substituted benziminiazoles as well.

Condensation of 4-Substituted o-Phenylenediamines with Two Moles of Aromatic Aldehydes

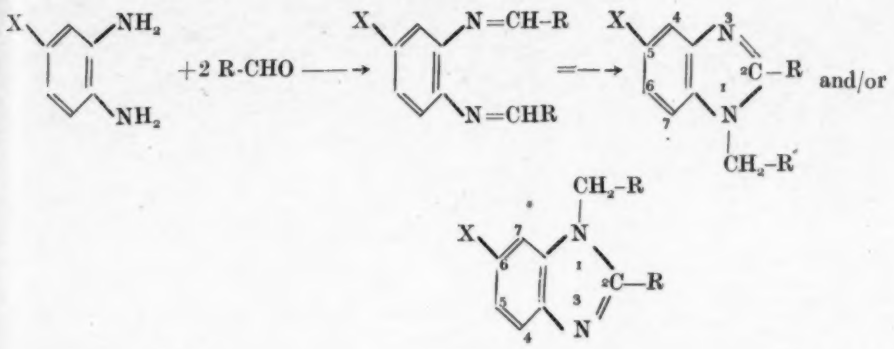
Past literature[27,33,37] on the condensation of substituted *o*-phenylenediamines with aldehydes is meagre and ambiguous. The condensation of 4-methyl-[38], 4-chloro-[39] and 4-nitro-[40] *o*-pheylenediamines with aromatic aldehydes was investigated following the standardised procedure with slight modifications. In general, the results obtained corroborated the conclusions arrived at in the condensations with the simple diamine. This indicates that the substituent in the aldehyde has a predominating influence on the reaction.

Appreciable amounts of 2-substituted benziminazoles have been isolated in the condensation of the chloro- and nitro-diamines with a number of aldehydes including the hydroxy- and amino-substituted ones, indicating thereby the significant influence exerted by chloro and nitro groups present in the diamine nucleus.

Condensation of the nitrodiamine with aldehydes afforded, in addition to the benzi-minzaoles, mono- and di-anils in a number of cases, thus providing strong support to the stepwise mechanism for the formation of benziminazoles, proposed earlier.

Isomerism of 1,2-Disubstituted Benziminazoles from 4-Substituted o-Phenylenediamines

The dianil (V), formed from one mole of a 4-substituted diamine and two moles of aldehyde on cyclisation gives rise to two isomeric 1,2-disubstituted benziminazoles (VI) and (VII).



Thus arises the problem of fixing the position 5 or 6 of the aromatic substituent in the 1,2-disubstituted benziminazoles from 4-substituted *o*-phenylenediamines and aldehydes. By synthesising the 5- and 6-isomers, (VI) and (VII), adopting unambiguous methods and comparing them with the condensation product (in the case of benzaldehyde), it has been found that the condensation of 4-methyl-*o*-phyenylenediamine gives rise to 6-methyl-1,2-disubstituted benziminazoles[41], the 4-chloro-, 5-chloro[42] and the 4-nitro-diaminer to 6-nitro-[43] disubstituted benziminazoles.

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Isolation and Reactions of Steroid Sapogenins

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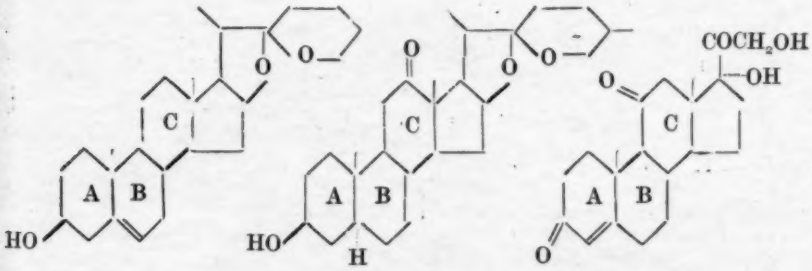
The discovery of the beneficial effects of cortisone and its related products has brought to light the importance of the chemistry of the steroid sapogenins. Attempts were at first made for preparation of these products starting from various classes of steroid bodies, but very soon it was realised that for such preparations, the steroid sapogenins ware undoubtedly the most favourable starting material. Most of the steroid sapogenins may profitably be utilised for the preparation of such hormones provided that these are economically available in quantities. In this respect two sapogenins, viz., diosgenin and hecogenin, have come to much prominence in recent years. Diosgenin is represented as 22a spirost-5-en-3β-ol(I) and hecogenin as 5 α- 22a-spirostan-3β-ol-12-one (II). In view of an oxygen function in the ring C of hecogenin and the availability of this product in the wastes of sisal fibre industry, it owes an apparent advantage over diosgenin for the preparation of cortisone (III), which has a keto group in the 11-position in ring C. It may, however, be noted that hecogenin content of *Agave* (Sisal) plants is usually below 0.3%, whereas the diosgenin content of *Dioscorea* yams may even be above 5%. Moreover, the shifting of the keto group from the 12-position of hecogenin to the 11-position requires a number of steps comparable to some extent with the introduction of the keto group in the 11-position of diosgenin. As regards the preparation of hormones having no oxygen function in ring C, diosgenin is undoubtedly a much better starting material from all standpoints.



In view of the importance of steroid sapogenins[1] in the preparation of useful hormones, extensive investigations were carried out in various countries for finding out suitable plant sources for these products.

An exhaustive survey[2] of the Indian *Dioscorea* yams was undertaken in this laboratory with a view to locating rich sources for diosgenin. Diosgenin is the principal sapogenin

of the yams of *Dioscorea* plants (Family: Dioscoreaceae) and was first isolated from *Dioscorea tokoro* Makino[3-4] of Japan and later Marker and his collaborators[3-5] isolated it from a number of Mexican *Dioscorea* plants.

The *Dioscorea* plants are climbers. The plants have often prickly stems. The leaves are reticulate and petiole is often angled. Flowers are small, unisexual, dioecious or monoecious in separate spikes. The yams (tubers) of these plants vary from species to species as regards size and shape. Generally the tubers are soft with white flesh, although there are others with hard woody tubers. The edible varieties are used as cheap substitutes for potatoes. Sometimes inedible tubers are also taken by Santhals, Kols, and hill tribes in our country after proper processing to remove poisonous constituents like alkaloids and saponins. The method used generally is a thorough washing of the sliced or macerated tubers with hot water. The product after drying is usually obtained as a white powder which is used like flour.

Notable poisonous yams amongst the Indian *Dioscorea* plants are those of *D. hispida*, *D. deltoidea*, and *D. prazeri*. *D. hispida* is known in Western India as *marapashpoli* or deadly strangle cake on account of its poisonous character. The Bhils poison tigers by placing pounded tubers on the carcases of kills. *D. prazeri* is called *Kencheong* by the Lepchas and *kukur torul* or dog's yam by the Paharias. Indian names of *D. deltoidea* are *kins*, *kildri*, *kithi*, *krithi*, *krits*, *krish*, etc. Both *D. prazeri* and *D. deltoidea* are used as soap, specially for washing wool and silk also for washing hair to remove lice, and as fish poisons for catching fish. Some of the *Dioscorea* yams are used in the indegenous system of medicine as diuretic.

At least thirty differeut species of *Dioscorea* plants grow in different parts of this country, some in the hills, others in the plains but mostly in jungles. Some of the edible varieties are even cultivated and yams of these are sold in local markets. Some of the common species are *D. alata*, *D. anguina*, *D. bellophylla*, *D. daemona*, *D. bulbifera*, *D. deltoidea*, *D. glabra*, *D. hispida*, *D. Hookeri*, *D. hamiltonii*, *D. jacquemontii*, *D. kamonensis*, *D. lepcharum*, *D. oppositifolia*, *D. pentaphylla*, *D. prazeri*, *D. pubera*, *D. sativa*, *D. scrotichinii*, *D. tomentosa*, *D. trinerva*, *D. wallichii*, and *D. wattfi*. Yams of twenty different species of these plants were collected mostly through various forest offices and examined in our laboratory. These are: *D. alata*, *D. glabra*, *D. oppositifolia*, *D. wallichii*, *D. bellophylla*, *D. pubera*, *D. nummularia*, *D. aculeata*, *D. esculenta*, *D. hispida*, *D. pentaphylla*, *D. tomentosa*, *D. prazeri*, *D. bulbifera*, *D. deltoidea*, *D. sativa*, *D. glauca*. Of these, the first eight belong to the right-twining sub-group and the rest to the left-twining sub-group. The last one, *D. glauca*,[6] although regarded as a variety of *D. nummularia*, is found to have close similarity with *D. prazeri*. Three of the yams could not be identified properly.

The air-dried powdered yams were extracted successively with petroleum ether (b.p. 40-60°), chloroform, ethyl acetate, and ethanol in an all-glass soxhlet extractor. The solvent-free residue obtained from end fraction was tested for saponin by treatment with water when a comparatively stable froth with characteristic honey-comb structure was produced. Such solutions were subjected to haemolytic test for saponin as also tested for their fish-poison character against gold fish (*Carassius auratus*).

Isolation of the sapogenins[7] from the various yams was initially carried out by extracting the air-dried, powdered yams with ethanol followed by defatting the alcoholic extract with ether, hydrolysis with ethanolic hydrochloric acid, and final extraction with ether. Both *D. prazeri* and *D. deltoidea* yielded rather high percentages of extractives.

On account of this and other factors, the extraction of the powered yams in a soxhlet is associated with considerable difficulties. These were to some extent obviated by carrying out some modifications in the procedure for extraction. It was ultimately possible to further simplify the procedure[8]. For this purpose, the ethanolic extract of the yams after removal of the solvent was treated with sufficient water to produce a colloidal suspension of the saponin. The product was defatted by gentle refluxing of the aqueous suspension with petroleum ether (60-80°), hydrolysed with aqueous hydrochloric acid, and extracted with benzene. Hydrolysis and extraction of diosgenin were carried out in a single stage by gentle refluxing of the defatted product in presence of hydrochloric acid and benzene. The residue obtained from the benezene extract after proper purification gave pure diosgenin. Although Wall and his collaborators[9] have found it convenient to isolate the sapogenins from the fresh plant materials, we like to recommend the use of dried powdered yams in the case of isolation of diosgenin from *D. prazeri* and *D. deltoidea*.

More recently, Vishwapal *et al*[10]. claimed a method of isolation of diosgenin from *Dioscorea* yams although this method was developed by Rothrock *et al*[11]. earlier. The method consists in hydrolysing the coarsely powdered, air-dried yams with aqueous hydrochloric acid, washing the product free of acid, drying, and extracting in a soxhlet with petroleum ether (40-60°). This method was described by the American workers as a general procedure for isolation of diosgenin from *Dioscorea* yams, using *D. barbasco* as a typical case and was utlised by Vishwapal *et al*.[10] for isolation of diosgenin, whereas in this laboratory, the same was applied to *D. prazeri*.[12] It may be mentioned in this connection that hydrochloric acid has an adverse effect on diosgenin, since according to Peal[13] it changes into 25D-spirosta–3, 5-diene when heated with ethanolic hydrochloric acid. In the method developed in this laboratory[8] in the hydrolytic stage, as soon as any diosgenin is formed it is immediately extracted with benzene and is thus removed from the field of action of hydrochloric acid.

The diosgenin content of the different species of India *Dioscorea* yams has been found to vary noticeably. The average yields of diosgenin from *D. esculenta*, *D. prazeri*, *D. deltoidea*, and *D. glauca* are 0.15-0. 2%, 2.5-3.5%, 4-6%, and 4.5-5% respectively. A critical account of the comparative position of *D. deltoidea* and *D. prazeri* with regard to production of disogenin from Indian resources was published by the present authors.[8] Although *D. deltoidea* contains a much higher percentage of diosgenin than *D. prazeri*, in various other respects the latter is much more useful. *D. glauca* being very similar to *D. prazeri* has all the advantages of the latter, but in addition the yield of diosgenin is comparable to that of *D. deltoidea*[8]. Moreover, cultivation of *D. glauca*[14] appears to be much more easy. For these reasons *D. glauca* offers a considerable promise as an economic source of diosgenin.

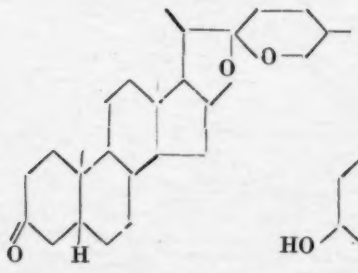
It has been observed, particularly during powdering, that the dust is rather toxic when the yams contain a high percentage of the saponin. It usually causes bad sneezing and produce symptoms similar to catching cold with or without temperature and may even cause gastrointestinal disorder.

The chief constituent of the *Dioscorea* yams is a starchy matter. Tubers of *D. deltoidea* were found to contain 37-38% of starch and *D. prazeri*, 39-40%[15]. In view of this it was found desirable to explore the possibility for utilisation of this starchy matter. Most of the starch was found to be present in the thimble after ethanolic extraction of the saponin by the method of Chakravarti *et al*.[7] and can be utilised for any suitable purpose. In the

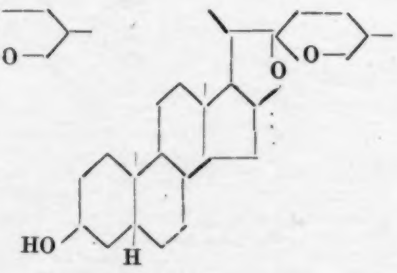
method of Rothrock *et al.*[11] during hydrolysis of the plant material with aqueous hydrochloric acid, considerable amounts of sugar were, however, found to be formed[15] mostly from the starchy matter and some from the saponin. In this method very little unhydrolysed starch could be found in the plant residues after extraction of diosgenin. In the aqueous hydrochloric acid mother liquor, in addition to the sugars, some amount of laevulinic acid was found to be present, formed obviously by the action of hydrochloric acid on the sugars. By following the improved procedure for preparation of laevulinic acid[16], it was possible to isolate this acid in good yields from the acid liquors after conversion of the remaining sugar into the acid by further heating of the acid liquor.

It has already been stated that hecogenin, another important sapogenin, is present in many *Agave* plants. In this connection an investigation on the sapogenin contents of some local *Agave* plants was carried out. It was found that *Agave cantala* and *Agave sisalana*[17] contain 0.15% and 0.10% hecogenin respectively.

Although the usual method for hydrolysis of the saponin into the sapogenin consists in heating with aqueous hydrochloric acid, the same splitting can be brought about by saponases present in some plants. In the latter case, the hydrolysis may be effected at the room temperature. Considerable amounts of saponases are present in *Agave* leaves due to which hecogenin may be obtained by autolysis. Morever, *Agave* juice, rich in saponases, can be utilised for hydrolysis of glycosides of other plants. For instance, it has been utilised for isolation of diosgenin from *Dioscorea* tubers[18]. This method was tried in this laboratory in the cases of *D. prazeri* and *D. deltoidea*. For this purpose, *D. prazeri* and *D. deltoidea* were separately treated with pressed-out liquor of *Agave cantala* leaves for a definite period. It was then filtered, dried, and extracted with petroleum ether in a soxhlet. The petroleum ether extract after removal of the solvent was chromatographed over Brockmann alumina in each case. The products obtained in the case of *D. deltoidea* were identified as diosgenin and smilagenone and those in the case of *D. prazeri* as diosgenin and epi-smilagenin[19]. The formation of smilagenone (IV) and epi-smilagenin(V) under such conditions is quite interesting and in this respect it has been found desirable to make a thorough study of this reaction using only *Dioscorea* yams in the absence of *Agave* juice.



(IV)



(V)

With the avove object, fresh yams of *D. prazeri* or *D. deltoidea*, after being cut to pieces and crushed, were kept with excess of water for periods ranging from a few weeks to several months. The product was filtered, dried, and extracted with petroleum ether in a soxhlet. A white crystalline product was obtained, which on chromatography over Brockmann alumina using various mixtures of petroleum ether and benzene furnished

mainly smilagenone (IV), m.p. 188-89° [semicarbazone, m.p. 222-23° (dec.); oxime, m.p. 180° (dec.); 2, 4-dinitrophenylhydrozone, m.p. 212-13° (dec.)] and epi-smilagenin (V),[20] m.p. 220-22° (acetate, 163-64°, benzoate, 189-90°). The plant residues left after the extraction were hydrolysed with aqueous hydrochloric acid; the hydrolysed product was dried and extracted with petroleum ether. The residue obtained from the latter extract was chromatographed as in the previous cases when only diosgenin could be isolated, the yield varying considerably depending on the period of contract with water and the yields of smilagenone and epi-smilagenin isolated in the previous stage.

When the yams are kept with water for one or two weeks, the yields of smilagenone and epi-smilagenin are low. When the fresh yams (crushed) of *D. prazeri* are kept with water for about three months, the change is almost complete. Further, it is found that longer period of contract with water favours the formation of epi-smilagenin, whereas the shorter period favours the formation of smilagenone. It may be mentioned in this connection that Rothrock *et al*[21]. reported the isolation of $\triangle^4$ diosgenone in one case of microbiological hydrolysis of *Dioscorea* tubers, although in general, they found that the saponins in *Dioscorea* tubers were cleaved into diosgenin and the sugar moieties by microbiological hydrolysis. Marker *et al*.[22], however, reported the formation of diosgenin, smilagenin, and epi-smilagenin from $\triangle^4$-dehydrotigogenone, administered to a dog on biscuit diet.

To ascertain whether the transformation in the steroid moiety of the saponin takes place in the glycosidic stage or in aglycone stage, experiments were carried out by keeping finely dispersed diosgenin in contact with sufficient amounts of waste liquor, obtained, as stated above, after separation of smilagenone etc. by keeping *Dioscorea* yams in contact with water for about five months. A control-specimen consisting of the waste liquor, without addition of any diosgenin, was also kept. After three months both were filtered, dried, and extracted with ether. The residue from the ethereal extract was chromatographed as above, when only unchanged diosgenin could be obtained from the main lot and practically nothing from the control. It is thus evident that the change of the diosgenin moiety of the *Dioscorea* saponin into epi-smilagenin does not take place after the hydrolysis. The fact that only diosgenin, unassociated with any epi-smilagenin, can be obtained from the plant material by hydrolysis with acids after thorough extraction in a soxhlet for epi-smilagenin, as stated above, indicates that the saponin with diosgenin as the aglycone changes into another with epi-smilagenin as the aglycone as a slow reaction and that the newly formed saponin readily hydrolyses into epi-smilagenin and the sugars.

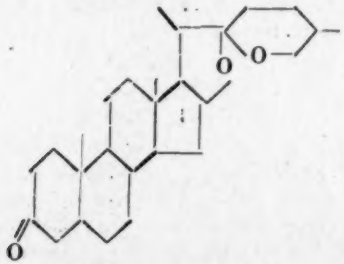
The conversion of diosgenin into pseudodiosgenin constitutes the first step in the preparation of steroid hormones from diosgenin. In this respect it was found desirable to study this conversion properly in this laboratory. The usual method[23] consists in heating the sapogenin with five times its weight of acetic anhydride in a sealed tube at 195-200°. After a number of trials in this laboratory[25], the optimum condition for the conversion was found to be a temperature of 192°, the period of heating being ten hours. The reaction could also be carried out conveniently in a glass tube, closed at one end and stoppered tightly by a cork at the other end, immersed in an oil-bath heated to the desired temperature instead of carrying out the reaction in a sealed tube in a bomb furnance. Lastly, as it appeared that pressure had very little effect on this reaction, the conversion was carried out by the present authors[25] in an open system using glycerol triacetate (triacetin) as a high-boiling medium. For this purpose, diosgenin was refluxed for 10 hours with acetic anhydride and sufficient amount of glycerol triacetate. The temperature of the liquid mixture was kept at 192° throughout the period. The product, a dark-coloured liquid,

was treated with water when pseudodiosgenin diacetate crystallised out. The product after crystallisation from methonol gave pure pseudodiosgenin diacetate, m.p. 99-100°.

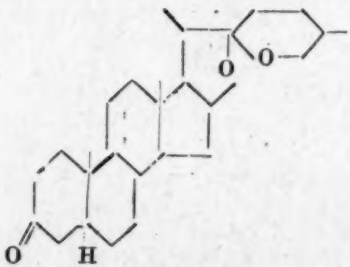
Reference may be made in this connection to the various other modifications carried out in the method of conversion of sapogenins into pseudosapogenins as performed in different laboratories. Marker and Rohrman[26] reported the isomerisation of sarsasapogenin into pseudosarsasapogenin by using various other acid anhydrides, such as, propionic anhydride, succinic anhydride, butyric^{n} anhydride, in place of acetic anhydride. In the case of butyric^{n} anhydride (b.p. 198°) the isomerisation was effected by ordinary refluxing. The yields were, however, quite variable and rather low. Good yields of pseudodiosgenin were obtained by Cameron *et al.*[27] by heating diosgenin with refluxing octanoic^{n} acid (b.p. 237°) containing a little acetic anhydride. Amongst other modifications for the conversion of sapogenins (spirostans) to pseudosapogenins (furostenols), mention may be made of Gould *et al.*[28] using catalyst like hydrochloric acid, *p*-toluenesulphonic acid, aluminium chloride, etc. under reflux condition and of Dauben and Fonken[29], using acetic anhydride containing pyridine hydrochloride for the same conversion.

Our method[25] for the conversion of diosgenin to pseudodiosgenin was found to be suitable also for tigogenin which, when mixed with acetic anhydride and sufficient glycerol triacetate, on refluxing at 192° for 10 hrs. gave a dark-coloured liquid. The product on hydrolysis with alcoholic potassium hydroxide yielded pseudotigogenin, m.p. 190-94°. As glycerol triacetate has no catalytic action, it may be replaced by other similar high-boiling solvents.

While studying the chemical properties of diosgenin for its proper utilisation in the preparation of hormones, work was carried out on the action of Raney nickel on diosgenin at different temperatures. For this purpose diosgenin in xylene solution was heated under reflux in presence of Raney nickel catalyst according to the method of Chakravarti and Robinson[30] for conversion of strychnine into neostrychnine. On working up, major portion of diosgenin was, however, recovered unchanged. The reaction was then carried out at a higher temperature using *p*-cymene as a solvent instead of xylene. For this purpose, diosgenin, dissolved in freshly distilled *p*-cymene, was mixed with Raney nickel, previously washed with *p*-cymene, and refluxed for twelve hours. The product was filtered. The filtrate was distilled in steam to remove the solvent. The residue thus obtained after separation of water was taken up in ether. The residue from ethereal extract was chromotographed over Brockmann alumina using mixtures of petroleum ether and benzene as eluent, when diosgenone (VI), m.p. 185-86°, was obtained as the major product[31]. On repeating the experiment with excess of Raney nickel, tigogenone (VII), m.p. 206-207°, was obtained. The latter product formed a semicerbazone, m.p. 263° (dec.); oxime, 250-52° (dec.) and 2, 4-dinitrophenylhydrozone, m.p. 258° (dec.) and on hydrogenation in glacial acetic acid it yielded dihydrotigogenin, m.p. 166-68°.



(VI)



(VII)

The reaction with Raney nickel was also carried out with other steroid sapogenins. Under similar conditions, both smilagenone and epi-smilagenin yielded tigogenone and hecogenin gave hecogenone, m.p. 235-36°. It was also observed that when cholesterol was similarly heated under reflux with Raney nickel in *p*-cymene solution, Δ^4-chloestenone was the main product. It may be mentioned in this connection that Romo[32] reported the formation of 3-oxo-Δ^4-steroids by oxidation of 3-hydroxy-Δ^4-steroids with Raney nickel in the presence of acetone or methyl ethyl ketone as hydrogen acceptor, but no reaction occurred with isolated hydroxyl compounds or with 3-hydroxy-Δ^5- steroids. According to Kleiderer and Kornfold[33], cholesterol is converted, however, to Δ^4-cholestenone when cholesterol is heated in toluene solution in presence of cyclohexanone as hydrogen acceptor.

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Some Observations on the Kinetics and Mechanism of Inorganic Reactions in Solution

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Investigations have been carried out on the kinetics of dissociation in acid ($HClO_4$) medium of the chelate complexes formed by chromium (III) and cobalt (III) with biguanide, hexyl^n biguanide, and phenylbiguanide. In acid medium the dissociation reaction can be represented as:

$$\underset{\text{(i)}}{M(BH)_3^{3+}} + H^+ \longrightarrow \underset{\text{(ii)}}{M(BH)_2^{3+}} \quad BH_2^+$$

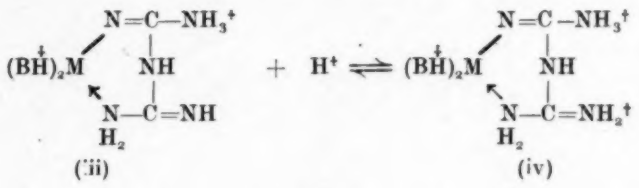
where M stands for Cr (III) or Co (III) and BH for a molecule of any biguanide. It is probably needless to point out that the species (*ii*) will also have two molecules of water (not shown) in order to satisfy the co-ordination number six of the metal. The species (ii) will further dissociate in a similar manner affording the mono-(biguanide) complex, which in turn will dissociate to the metal ion (aquated). It has been observed, however, that the different steps occur in different acid concentrations, a fact to be expected from the large differences in the formation constants of the mono, bis, and tris complexes in general[1,2]. Even in the acidity regions, where the consecutive steps occur, the second step is, however, generally very much slow so that the kinetics of the first step can be easily followed, at least in the initial stages of the reaction. The spectrophotometric method, which has been used for following the rates of these reactions, makes use of the sufficiently large differences in the molar absorbance indices of the tris, bis and mono complexes at the λ_{max} which is almost the same (within about 10-20 mμ) for all the species. Measurements of the rate at different acid concentrations indicate that in all the cases, where the reaction could be conveniently followed (Table I), the following rate expression holds good:

$$\text{Rate} = k_{obs}\,[\text{Complex}]\,[H^+] \qquad \text{(I)}$$

temperature and ionic strength being maintained constant, the latter with sodium perchlorate. It has been further observed that for both the chromium (III) and cobalt (III) tris complexes, at any particular acid concentration, ionic strength, and temperature, the rate decreases in the following sequence of the ligands:

Biguanide > Hexyl^n biguanide > Phenylbiguanide.

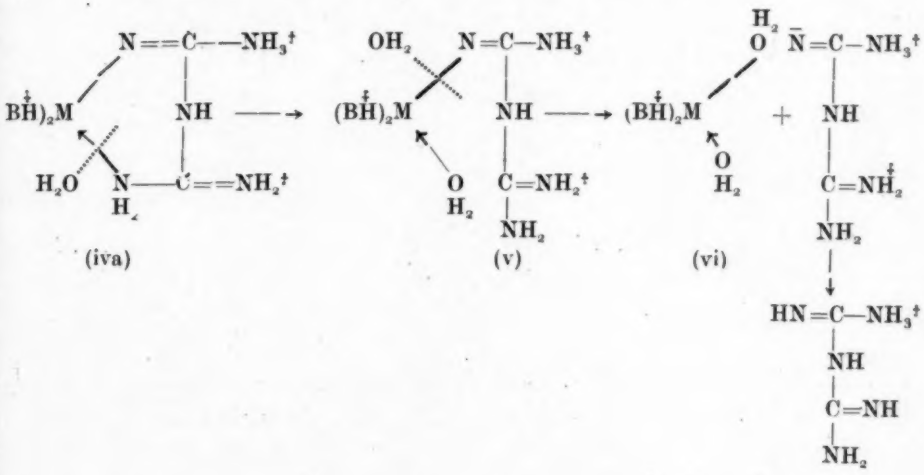
This is exactly the order of decreasing base strength of the ligands and also of the decreasing stability of the corresponding complexes[1-2]. (Quantitative data for the hexyl[n]biguanide complexes are not available in the literature, but these are expected to be intermediate between biguanide and phenylbiguanide complexes). This apparently paradoxical result, as reported above, namely, the greater liability of the more stable species, can be accounted for by a mechanism involving protonation of the complex-bound ligand prior to bond rupture, e.g.:



(ii) (iv)

i.e., $M(BH)_3^{3+} + H^+ \rightleftharpoons M(BH)_2(BH_2)^{4+}$

The structural formula (iii) for the metal-biguanides has been well established by Rây *et al*[3,4]. It is clear that the species (iv) will have a greater tendency for bond rupture with the simultaneous entry of two water molecules, possibly in stages:



(iva) (v) (vi)

If k be the rate constant for the dissociation of the species (iv), it can easily be shown that

$$\text{Rate} = k.K\ [\text{Complex}]\ [H^+] = k_{obs}\ [\text{Complex}]\ [H^+] \qquad .. \qquad .. \qquad (II)$$

where K is the equilibrium constant for the formation of species (iv) from (iii) and H^+ ion. Since the value of K will depend on the base strength of the co-ordinated ligand (which will naturally be related to the base strength of the free ligand) the cause of greater liability of the more stable species is easily understood. It is further interesting to point out in this connection that tris-ethylenediamine-chromium (III) ion, $Cr(en)_3^{3+}$, dissociates over

thousand times slower[5] than the tris-biguanide-chromium (III) ion under comparable conditions, and from our own observations tris-ethylenediamine-cobalt (III) ion is not changed at all in 1*M* perchloric acid during a period of one week at *ca.* 32°. This is not unusual as in the ethylenediamine complexes the co-ordinated ligand possesses no free basic group and hence the protonation mechanism, outlined above, cannot operate; in these complexes (of ethylenediamine) protonation can occur only after bond rupture and not prior to that. Thus owing to the absence of the extra driving force favouring bond rupture, the complexes of ethylenediamine are much more inert than those of the biguanides.

Incidentally, our observations on the effect of salt concentration on the rate are also interesting. Using sodium perchlorate, lanthanum perchlorate, and mixtures of the two in various proportions, we have been able to make a set of observations on the rate at different ionic strength having the same perchlorate ion concentration and *vice versa*. The results indicated that the rate was increased by increase of the ionic strength as well as of the perchlorate-ion concentration. Similar observations, as reported in the literature, are too conflicting as some[6] claim that the effect of a salt on the rate of reaction between ions having similar charge is due to its influencing the ionic strength in general, whereas others[7] believe this to be due to the concentration of the oppositely charged ion, an increase of which favours the approach of two ions of like charge necessary for the formation of the activated complex in the transition state.

No less interesting are our observations on the dissociation of chromium (III)-tris-biguanide complex in alkaline medium, where the experimental observations indicate a rate expression of the following type, in the range of 0.1 to at least 1*M* sodium hydroxide solution:

$$\text{Rate} = k'_{obs}\,[\text{Complex}]\,[OH^-)^{-1} \qquad \ldots \qquad \text{(III)}$$

Since the reaction in 0.1 *M*-NaOH is only about one-third as fast as in 0.01*M* perchloric acid, both at an ionic strength of 1*M* sodium perchlorate and at the same temperature (35.5°), the inverse dependence of the rate on the OH^- ion concentration (vide equation III) cannot be due to the mechanism of dissociation in alkaline medium being the same as the one in acid solutions. In this case (alkaline media), we believe that the following mechanism operates. In alkaline medium the complex cation exists as the anhydro-base which dissociates by a protonation mechanism, e.g.:

$$\underset{\text{(vii)}}{Cr(BH)_3^{3+}} + 3\,OH^- \longrightarrow \underset{\text{(viii)}}{CrB_3} + 3H_2O$$

$$\underset{\text{(viii)}}{CrB_3} + H^+ \rightleftharpoons \underset{\text{(ix)}}{CrB_2(BH)^+}$$

$$\underset{\text{(ix)}}{CrB_2(BH)^+} \xrightarrow{\text{slow}} \underset{\text{(x)}}{CrB_2^+} + BH$$

On the basis of the above mechanism the complete rate expression will be:

$$\text{Rate} = k'.\,K'.\,K_W\,[\text{Complex}]\,[OH^-]^{-1} \quad ..$$

$$= k'_{obs}\,[\text{Complex}]\,[OH^-)^{-1} \quad .. \quad \text{(IV)}$$

where k' is the rate constant for the change of species (ix) to (x), K' is the equilibrium constant for the formation of species (ix) from (viii) and H^+ ion, and K_w is the ionic product of water. It may be pointed out that the anhydro-base is known and its formation in alkaline solution has also been indicated during the present investigations by an increase in the molar absorbance index of the complex. These results therefore indicate the kinetic stabilizatian of chromium(III)-tris-biguanide in alkaline media, an observation of great significance as this explains nicely the fact that this species is formed from freshly precipitated chromium (III) hydroxide and biguanide in strongly alkaline media and is hydrolysed to the bis-complex only in an alkaline medium buffered with excess of ammonium salt[8]. As the phenylbiguanide complex (0.001 *M*) is precipitated even in dilute alkali medium (0.01 *M* NaOH), measurements of the rate could not be made in this case. The behaviour of the phenylbiguanide complex is, however, expected to be very similar and it is known that chromium(III)-tris-phenylbiguanide complex is also prepared in hot strongly alkaline medium[9]. It has further been observed that cobal(III)-tris-biguanide is exceedingly inert in alkaline media to resist any change over a period of one week at 32° in 0.01 to 2,0 *M* sodium hydroxide solutions; cobalt (III)-tris-ethylenediamine complex is also known[10] to dissociate immeasurably slowly under similar conditions and measurable rate is observed only from 70° onwards.

The activation energies of the various reactions studied have also been determined graphically as usual by making use of the Arrhenius equation. These values are recorded in Table I along with a few typical rate constants.

TABLE I

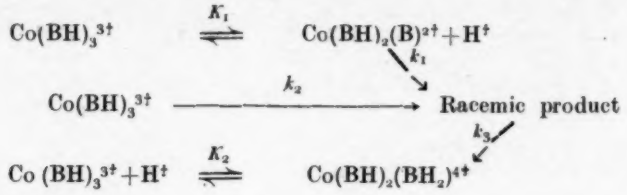
Kinetics of dissociation of Cr (III) *and* Co (III) *complexes.*

Complex: 0.001 *M*. Ionic strength = 1 *M* ($NaClO_4$). Temp. = 35.5°.
[BigH = Biguanide. PhbigH = Phenylbiguanide. HxbigH = Hexyl[n] biguanide].

Complex.	$HClO_4$.	Observed rate constant $\times 10^3$ min^{-1}	Activation energy, (k. cal).
	Dissociation in acid.		
$Cr(BigH)_3^{3+}$	0.01 *M*	73	12.3
$Cr(BigH)_2^{3+}$	1.00	4	19.9
$Cr(PhbigH)_3^{3+}$	0.01	20	17.0
$Cr(PhbigH)_2^{3+}$	1.00	3	24.0
$Cr(HxbigH)_3^{3+}$	0.01	24*	16.6
$Co(BigH)_3^{3+}$	0.10	90	13.6
$Co(PhbigH)_3^{3+}$	0.10	9	13.5
$Co(HxbigH)_3^{3+}$	0.05	17*	11.6
	Dissociation in alkali. NaOH.		
$Cr(Big)_3$	0.2 *M*	33	24.8

* These runs were carried out in solutions which did not contain any indifferent electrolyte ($NaClO_4$) for ionic strength adjustment as these complexes were found to be salted out by $NaClO_4$.

In this connection it may be interesting to discuss the observations reported by Rây and Dutt[11] much earlier on the kinetics of racemization of the cobalt (III) complex (tris) of biguanide. A critical examination of their data indicates that the rate is either independent of H^+ ion or else retarded or accelerated by it, depending on the range of acidity. These results seem to suggest that the complex can racemize by three distinct paths as shown below:



where k's stand for the reaction rate constants and K's for respective equilibrium constants. On the basis of the above mechanism it can be shown that

$$\text{Rate} = \{k_1 K_1/[H^+] + k_2 + k_3 k_2[H^+]\}[\text{Complex}] \quad \ldots \quad (V)$$

From equation (V) it follows that, for proper values of the constants, the rate will be either independent of H^+ ion or else there will be retardation or acceleration of the reaction by H^+ ion depending on the acidity range. Although the intramolecular mechanism involving distortion of the molecule without any bond rupture, suggested by Rây and Dutt[11], is likely to operate for the species $Co(BH)_3^{3+}$ and $Co(BH)_2(B)^{2+}$, the protonated species, $Co(B_2H)_2(BH_2)^{4+}$, is not unlikely to recemize by bond rupture, at least passing through a five-co-ordinated intermediate due to fission of the chelate ring of the protonated ligand.

A discussion of some of our recent observations, still in progress, on the mechanism of reduction of rhenium (V) to rhenium (IV) by Sn (II) in hydrochloric acid medium seems pertinent. On treating a solution of potassium perrhenate in hydrochloric acid medium with excess of Sn (II) chloride, a green color is formed instantaneously due to reduction of rhenium (VII) to rhenium (V), which is further reduced rather slowly to rhenium (IV)[12]. In solutions containing over $3M$ hydrochloric acid, the rhenium (IV) remains in true solution exhibiting a brownish green colour. We have now made a series of observations on the kinetics of this step to find out the effects of the different species involved in this system on the rate of this reduction process. Our results are in agreement with the following rate expression:

$$\text{Rate} = k''_{\text{obs}}\,[\text{Re(V)}]\;\;[\text{Sn(II)}]^{0.5}[\text{HCl}] \quad \ldots \quad (VI)$$

These results can be interpreted on the basis of an atom-transfer mechanism as outlined below:

$$Cl_5ReO^{2-} + H_2SnCl_4 \xrightarrow{k_1} Cl_5Re(OH)^{2-} + HSnCl_4$$

$$Cl_5ReO^{2-} + HSnCl_4 \xrightarrow{k_2} Cl_5Re\,(OH)^{2-} + SnCl_4$$

Making use of the steady state assumption, it can be shown that

$$\text{Rate} = 2k_1[(\text{Re(V)}]\ [H_2SnCl_4] \quad .. \quad .. \quad \text{(VII)}$$

If we now assume that Sn (II) is present in the experimental medium (3 to 6 M-HCl) chiefly in a binuclear form, $H_2Sn_2Cl_6$, which is involved in equilibria of the following types:

$$H_2Sn_2Cl_6 \rightleftharpoons 2HSnCl_3, \text{ and}$$

$$HSnCl_3 + HCl \rightleftharpoons H_2SnCl_4$$

$$K' = [HSnCl_3]^2 / [H_2Sn_2Cl_6]$$

and $$K'' = [H_2SnCl_4] / [HSnCl_3] / [HCl]$$

then since,

$$[H_2SnCl_4] = K'^{0.5} \cdot K'' \quad [H_2Sn_2Cl_6)^{0.5}[HCl]$$

$$= 2^{-0.5} \cdot K'^{0.5}\ K''\ [\text{Sn(II)}]^{0.5}\ [HCl] \quad .. \quad .. \quad \text{(VIII)}$$

we get from equations ((VII) and (VIII):

$$\text{Rate} = 2^{0.5} \cdot K^{0.5} . K'' k_1[\text{Re(V)}]\ [\text{Sn(II)}]^{0.5}[HCl]$$

$$= k''_{\text{obs}}\ [(\text{Re(V)}]\ [\text{Sn(II)}]^{0.5}\ [HCl] \quad .. \quad \text{(IX)}$$

where [Sn (II)] represents its total concentration in the system.

The mechanism, just outlined above, is in agreement with the well-established formulas of rhenium (V) and rhenium (IV) species likely to be involved under the experimental conditions[1,2]. Although we have so far no direct experimental evidence as to the binuclear nature of Sn (II) species in hydrochloric acid medium (3 to 6M), this is, however, the only simple way we can account for the 0.5 order dependence of the rate on Sn(II) concentration. It may be pointed out in this connection that although the reaction rate is hardly affected by the presence of potassium chloride (1 M) in the solution, it is somewhat retarded by lanthanum chloride and accelerated by potassium bisulphate. Further details of such effects are under investigation. The activation energy of the reaction has also been evaluated in the usual way and it comes out to be about 10kcal. At 35.5° the observed rate constant for 0.003M rhenium (V), 0.06M Sn(II), and 4M-HCl is 0.089 min^{-1}.

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Constitution of Gossytrin, A New Glycoside from the Flower Petals of *Hibiscus Sabdariffa*

T. R. Seshadri and R. S. Thakur

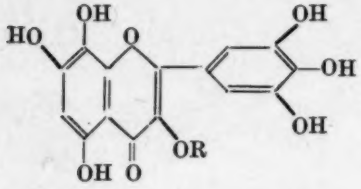
From the flower petals of *Hibiscus sabdariffa*, besides hibiscitrin (III), a new glucoside of gossypetin (II), gossytrin, has been isolated and found to be 3-glucoside by complete methylation followed by hydrolysis whereby is obtained gossypetin pentamethyl ether with the 3-hydroxyl free.

There are two varieties of *Hibiscus sabdariffa* (family, Malvaceae), rubes and albus; the stems, branches, and calyces of rubes are red in colour whereas those of albus are not. The flower petals are pale yellow in both cases, but in rubes, when once the flowers are plucked from the plant, the petals rapidly acquire a red colour owing to the formation of anthocyanin.

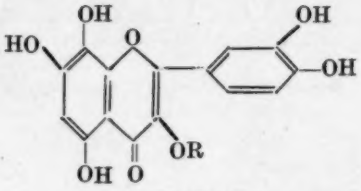
In the past (Perkin, *J. Chem. Soc.*, 1909, **95**, 1855; Rao and Seshadri, *Proc. Ind. Acad. Sci.*, 1942, **15A**, 148) the rubes variety of *Hibiscus sabdariffa* (dry petals) was examined and found to contain hibiscetin (I) and gossypetin (II), both of which occurred largely as glycosides. Hibiscitrin was the major component and its constitution was established (Rao and Seshadri, *ibid.*, 1948, **27A**, 104, 209) as hibiscetin-3-glucoside (III). In most of the samples examined, gossypetin was a minor entity; it was difficult to isolate its pure glycoside and characterise it correctly. Besides hibiscitrin, another trace component, shown to be present by the chromatographic study of Pankajamani and Seshadri (*J. Sci. Ind. Res.*, 1955, **14B**, 94), had also to be removed. The isolation of the gossypetin glycoside has been achieved in the course of the present work using separately fresh flower petals of rubes and albus varieties, both of which have hibiscitrin and the gossypetin glycoside, the *albus* petals having them in much lower proportion. After separating hibiscitrin by fractional crystallisation as far as possible, subsequent precipitation with neutral lead acetate and recovery of glycoside by decomposition of the lead salt with hydrogen sulphide yielded a product, which contained largely the gossypetin glycoside, and it could be purified by repeated fractional crystallisation.

The product had the composition $C_{21}H_{20}O_{13}$, $2H_2O$ and yielded, on hydrolysis with mineral acids, gossypetin (II) and glucose, one mole each. On complete methylation and subsequent hydrolysis, it formed a pentamethylgossypetin giving a violet-brown ferric reaction and melting at 226-28°. Among the pentamethyl ethers giving ferric reaction, it agreed with the 3-hydroxy compound; its identity was established by comparison with an authentic sample of 3-hydroxy-5,7,8,3′,4′-pentamethoxyflavone (Rao and Seshadri, *Proc. Ind. Acad. Sci.*, 1946, **24A**, 377), using colour reactions and U. V. and I.R. spectra. Hence it follows that it is a new glucoside analogous to hibiscitrin and is named gossytrin (IV). Earlier, two monoglucosides of gossypetin have been described: (*i*) gossypitrin (Neelakantam and Seshadri, *ibid.*, 1937, **6A**, 12; Rao and Seshadri, *ibid.*, 1939, **9A**, 177; Murti and Seshadri, *ibid.*, 1948, **27A**, 258), 7-glucoside of gossypetin present in Indian cotton flowers (*Gossypium herbaceum*) and (*ii*) gossypin (Rao and Seshadri, *ibid.*, 1946, **24A**, 377; 1947, **25A**, 397), 8-glucoside

of gossypetin, the main component of the petals of *Hibiscus vitifolius* and *H. esculentus* and an occasional component of the petals of *Gossypium indicum*. The position of the sugar unit appears to make a marked difference in the colour of the glucosides, their solubility in water, and their colour reactions. Gossypitrin (7-glucoside) is sparingly soluble and is yellow in colour. Gossytrin (3-glucoside) is more soluble than gossypitrin in water and less coloured (very pale yellow), whereas gossypin (8-glucoside) is quite soluble in water and has a golden yellow colour. Another marked difference is connected with the colour produced in alkaline buffer solutions. At *p*H 9.2, the 7-glucoside, gossypitrin, gives a yellow colour changing to deep emerald green and slowly fading to pale brown-yellow. Gossytrin yields first a yellow solution, becoming brown-red and slightly turbid. In the case of gossypin the alkaline solution is yellow and the colour stable for over 24 hrs.



(1: R=H)
(III: R=$C_6H_{11}O_5$)



(II: R=H)
(IV: R=$C_6H_{11}O_5$)

EXPERIMENTAL

Samples of albus and rubes varieties of *H. sabdariffa*, grown in the Delhi University nursery (1955), and fresh flower petals of *H. sabdariffa* rubes, kindly provided by the Indian Agricultural Research Institute, Delhi (1957-58), were separately examined.

Extraction and Isolation of the Glycosides (H. Sabdriffa *var. rubes*).—Fresh flower petals were collected daily and immediately put into ethanol. When sufficient quantity (1 kg.) was available, the petals were exhaustively extracted with boiling ethanol (1.5 litres; 3 × 24 hrs.). The alcoholic extract was concentrated to about 500 c.c. under reduced pressure and was repeatedly treated with petroleum ether to remove resinous matter, wax, and nonflavonoid pigments like chlorophyll. When the petroleum ether extracts were almost colorless, the concentrated alcoholic extract was extracted with ether to remove any free aglycones and allowed to stand saturated with ether in the refrigerator for a month. During this period a yellow solid separated, which was mostly hibiscitrin. It was filtered and the mother liquor was again concentrated under reduced pressure to half of the volume and allowed to stand in the refrigerator. In this way two more crops of the yellow solid (hibiscitrin) were obtained and then the residual mother liquor was treated with a neutral lead acetate solution. The resulting orange-yellow precipitate was filtered, washed with a water, ground up, suspended in warm ethanol, and H_2S passed through the suspension. After filtering lead sulphide, the deep yellow solution was concentrated under diminished pressure to a small bulk. On allowing it to stand after addition of dry ether, gossytrin separated as aggregates of tiny prisms. After further crystallisations from ethanol-ether mixture, the m.p. was 182-84°. (Found: C, 48.2; H, 5.0. $C_{21}H_{20}O_{13}$, $2H_2O$ requires C, 48.8; H, 4.7%). The glycoside gave the following colour reactions:

(1) Ethanolic ferric chloride-olive green colour; (2) magnesium and EtOH–HCl—pink; (3) ethanolic benzoquinone—brilliant red colour; (4) aqueous NaOH (4%)—green colour

which rapidly changed to pale red brown; (5) aqueous sodium carbonate (10%)—emerald-green, fading to yellowish brown (5-10 min.), finally became red-brown as in (4); (6) aqueous sodium bicarbonate (saturated)—yellow turning red-brown and turbid; (7) aqueous borax solution—clear yellow solution becomes orange in an hour, and stable.

The flower petals of the albus variety were extracted in a similar manner. The yield of gossytrin was very poor and hibiscitrin was predominantly the major entity.

Hydrolysis of Gossytrin.—The glycoside (0.2 g.) was gently boiled with 7% sulphuric acid (20 c.c.) for 2 hours and the product extracted with ether. The aqueous solution was neutralised with barium carbonate and filtered; the neutral solution was concentrated and tested for sugar by circular paper chromatography: R_f 0.53 using phenol, saturated with water (33-34°), and developed with aniline hydrogen phthalate solution. The same R_f was obtained for glucose under the same conditions.

The ether extract was concentrated and examined using circular paper chromatography; R_f 0.43 using water, saturated with phenol and 0.34 using phenol, saturated with water, at 33-34°, which agreed with those of gossypetin. All the colour reactions were also in close agreement with those of gossypetin. It melted at 311-12° and the m.p. was undepressed by an authentic sample of gossypetin.

For quantitative determination of sugar, the glycoside (39.1 mg.) was refluxed with 7% H_2SO_4 (7c.c.) for 2 hours and the aglucone was completely extracted with ether. The sugar solution was made to 10 c.c. and glucose estimated colorimetrically (Folin Wu's method): (Found: glucose, 32.7%. Monoglucoside requires glucose, 34.9%).

Complete Methylation and Hydrolysis.—The glycoside (0.4 g.) as fine powder was suspended in dry acetone (50 c.c.); potassium carbonate (2.0 g.) and excess of dimethyl sulphate (1.2 c.c.) were added and the mixture was refluxed for 60 hrs. It was then filtered and the acetone distilled from the filtrate. The semisolid residue was hydrolysed by boiling with 7% H_2SO_4 (50 c.c.) for 2 hrs. The solution was then extracted with ether and the crude methyl ether (0.15 g.) crystallised from methanol-ethyl acetate mixture yielding pale yellow flat needles, m.p. 224-26°; with ethanolic ferric chloride it gave a violet-brown colour; mixed m.p. with an authentic sample of 3-hydroxy-5, 7, 8, 3′, 4′-pentamethoxyflavone (m.p. 226-28°), prepared by the method of Rao and Seshadri (*loc.cit.*, p. 377), was undepressed.

I. R. spectra in chloroform of the two samples agreed and the main absorption bands in microns are: 3.25 (w), 6.19 (s), 6.32 (m), 6.60 (s), 6.81 (m), 6.94 (vw), 7.50 (m), 7.91 (s), 8.30 (s), 8.49 (w), 8.70 (m), 9.50 (w), 10.79 (w). U.V. spectra had in both cases λ_{max} 254 and 320 mμ; λ_{min} 240 and 290 mμ.

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On the Stereoselective Synthesis of Oestrone*

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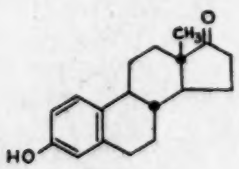
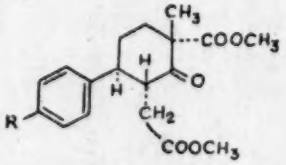
By application of the Robinson-Mannich reaction 6-*p*-anisyl-2-oxocyclohex-6-ene-1-acetic acid (VIa), 6-*p*-anisyl-2-oxo-3-methylcyclohex-6-ene-1-acetic acid (VIb), and the corresponding 3-alkoxycarbonyl derivatives (VIc, d, e, and f) have been prepared. The keto-acids (VIa and VIb) have been stereospecifically reduced to the saturated acids (VIIa and VIIb) and the saturated ester (VII c) stereospecifically converted into the keto-diester (IIb), the key intermediate from which Johnson *et al.* (*J. Amer. Chem. Soc.*, 1951, **73,** 5511; 1957, **79,** 1992) stereoselectively obtained natural oestrone.

With a view to developing a new route for the synthesis of oestrone (I), Banerjee and Dutta (*Science & Culture*, **1947**, **12**, 408) prepared the model keto-diester (IIa), which was later obtained in a purer form by Turner (*J. Amer. Chem. Soc.*, 1951, **73**, 3017) by a modified method. Its methoxy derivative (IIb) was also prepared by Turner (*ibid.*, 1951, **73**, 1284) and by Johnson *et al.* (*ibid.*, 1951, **73**., 5511; 1957, **79,** 1995), and the latter workers converted it stereoselectively to oestrone (I) (*loc. cit.*). An ingenious method was later developed by Bhattacharya and Sen Gupta (*Nature*, 1952, **170,** 710; this *Journal*, 1954, **31,** 327; cf. also Protiva *et al.*, *Chem. Listy*. 1953, **47,** 874; *Chem. Abs.*, 1955, **49**, 197) for the synthesis of this key intermediate (IIb). All these methods for preparation of the methoxy



(I)



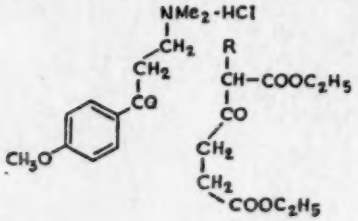
II a, R=H
b, R=OCH3

keto-diester (IIb), however, lack stereospecificity. It appeared to us that a stereospecific synthesis of this important intermediate (IIb) would render this route the most practicable one for oestrone. With this end in view we at first investigated the reduction of the model compounds (VIa and VIb) in which the $\alpha\beta$-unsaturated carbonyl group are in conjugation with the aromatic nucleus. The unsaturated keto-acid (VIa) was first prepared by Turner (*loc. cit.*) and later by Johnson *et al.* (*loc. cit.*). We have now prepared this keto acid (VIa) and its homologue (VIb) by a new method involving the Robinson-Mannich reaction.

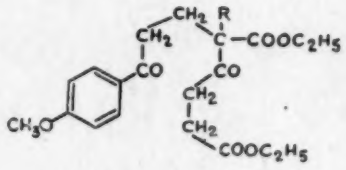
Condensation of β-dimethylamino-*p*-methoxypropiophenone hydrochloride (III) (Mannich and Lammering, *Ber.*, 1922, **55,** 3510) with diethyl β-oxoadipate (IVa) (Banerjee and Sivanandaiah, *J. Org. Chem.*, in press) in presence of dimethyl sulphate (cf. Johnson *et al.*, *J. Amer. Chem. Soc.*, 1953, **75,** 4996) gave the product (Va), which on refluxing with

* A preliminary communication appeared in *Tetrahedron Letters*, 1960, **5,** 20.

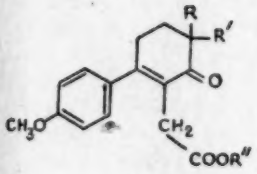
10% alkali under nitrogen smoothly underwent cyclisation, hydrolysis, and decarboxylation to furnish the unsaturated keto-acid (VIa) in 90% yield. Similarly when diethyl α-methyl-β-oxoadipate (IVb) was used, the unsaturated keto-acid (VIb) was obtained in 61% yield (see also Nasipuri *et al.*, *J. Chem. Soc.*, 1958, 2734; 1960, 1571 for similar reactions).



(III) (IV a): R=H
(IV b): R=CH$_3$



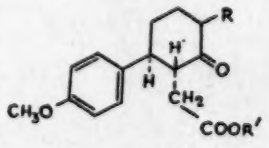
(V a): R=H
(V b): R=CH$_3$



(VI)

a, R=R′=R″=H.
b, R=CH$_3$, R′=R″=H.
c, R=R″=H, R′=COOC$_2$H$_5$.
d, R=CH$_3$, R′=COOC$_2$H$_5$, R″=H.
e, R=R″=H, R′=COOCH$_3$.
f, R=CH$_3$, R′=COOCH$_3$, R″=H
g, R=R″=CH$_3$, R′=COOC$_2$H$_5$
h, R=R″=CH$_3$, R′=COOCH$_3$
i, R=R′=H, R″=CH$_3$
j, R=H, R′=COOC$_2$H$_5$, R″=CH$_3$

The unsaturated keto-acids (VIa and VIb), on reduction with lithium and anhydrous ammonia (Banerjee *et al.*, *J. Amer. Chem. Soc.*, 1955, **77**, 408), gave the saturated *trans*-acids (VIIa and VIIb) stereospecifically in over 80% yield. The saturated acids on esterification furnished the esters (VIIc and VIId). On the other hand, when the methyl ester of (VIa) was reduced with 10% palladium-on-carbon, the product was a gum, presumably a mixture of *cis* and *trans* isomers, which on refluxing with 2% methanolic potassium hydroxide (Robins and Walker, *J. Chem. Soc.*, 1954, 3960) furnished the *trans*-acid (VIIa) in 63% yield.

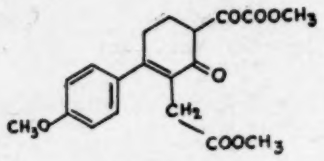


(VII)

a, R=R′=H
b, R=CH$_3$, R′=H
c, R=H, R′=CH$_3$
d, R=R′=CH$_3$

The desired reduction of the olefinic bond in the unsaturated keto-acids (VIa and VIb) by lithium and ammonia led us to investigate the possibility of effecting a similar reduction of the olefinic bond in the unsaturated keto-diester (VIh). We first attempted to prepare the latter by condensing the unsaturated keto-ester (VIi) with dimethyl oxalate

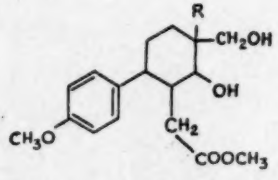
followed by pyrolytic elimination of carbon monoxide from the resulting glyoxalate (VIII) and subsequent methylation. Although the condensation proceeded in good yield, the elimination of carbon monoxide resulted in a substance of an extremely poor yield with an indefinite melting point.



(VIII)

The acid-esters (VIc, VId, VIe and VIf) could, however, be conveniently prepared starting from the condensation products (Va and Vb). Thus treatment of these with sodium ethoxide effected ring closure and partial saponification to yield 6-*p*-anisyl-3-ethoxycarbonyl-2-oxocyclohex-6-ene-1-acetic acid (VIc; 73% overall yield) and 6-*p*-anisyl-3-ethoxycarbonyl-2-oxo-3-methylcyclohex-6-ene-1-acetic acid (VId; 43% overall yield) respectively. Methylation of the methyl ester of (VIc) or esterification of (VId) furnished methyl 6-*p*-anisyl-3-ethoxycarbonyl-2-oxo-3-methylcyclohex-6-ene-1-acetate (VIg). Treatment of the condensation products (Va and Vb) with sodium methoxide caused *trans*-esterification and similarly afforded 6-*p*-anisyl-3-methoxycarbonyl-2oxocyclohex-6-ene-1-acetic acid (VIe; 77% overall yield) and 6-*p*-anisyl-3-methoxycarbonyl-2-oxo-3-methylcyclohex-6-ene-1-acetic acid (VIf; 61% overall yield) respectively.* The acid-ester (VIe) had earlier been prepared by a different method by Turner (*loc. cit.*, 15% yield) and by Johnson *et al.* (*loc. cit.*, 58% yield) and was converted by Turner (*loc. cit.*) into the saturated di-ester (IIb) in 39% yield. Further, Johnson *et al.* (*loc. cit.*) used the acid-ester (VIf) to conduct some exploratory experiments towards the synthesis of cortisone.

The unsaturated keto-diester (VIg) on treatment with lithium and ammonia remained unaffected. Next the acid-esters (VIc and VIf) were similarly treated and the resulting products were esterified and chromatographed over alumina. In each case one of the products isolated was the reduced keto-ester (VIIc and VIId) resulting through the loss of alkoxycarbonyl group. A second product isolated was presumably the alcohol (IXa or IXb) formed by reduction of both the carbonyl functions in (VIc or VIf). But the bulk of the material was the unchanged (VIj) or (VIh).

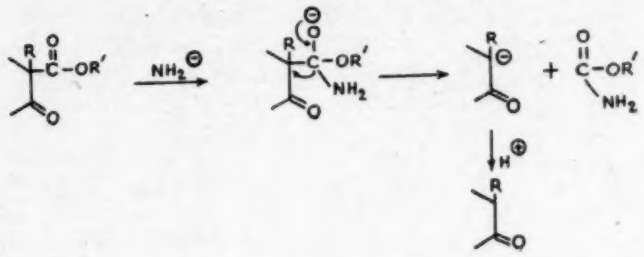


(IX a): R=H

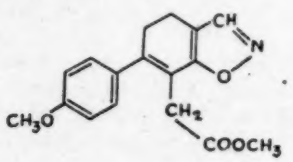
(IX b): R=CH3

*Subsequent to the publication of our preliminary communication (*loc. cit.*), Guha *et al.* reported the preparation of (VIe) and (VIf) by a similar procedure (this *Journal*, 1960, **37**, 267).

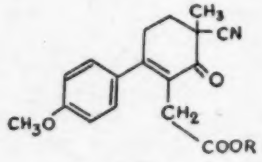
Elimination of the ester group in the reduction was obviously effected by the attack of the nucleophilic amide anion. When our investigations had been completed, Johnson *et al.* (*loc. cit.*) reported the reduction experiment with the acid-ester (VIf), prepared by a different method (*loc. cit.*) using lithium and ammonia, and observed that although the olefinic bond could be reduced, the reduction of the carbonyl function could not be prevented. But isolation of any specific product was not reported by them.



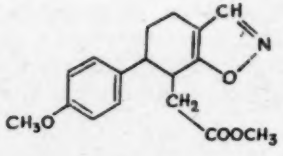
We next directed our attention to the preparation of the unsaturated cyano-keto-acid (XIa) with the expectation that the cyano group might survive the attack of the amide anion during lithium and ammonia reduction. The unsaturated keto-ester (VIi) could be converted *via* the isoxazole (X; 36% yield) to the cyano-keto-ester (XIb; 90% yield) by Johnson's procedure (*J. Amer. Chem. Soc.*, 1945, **67**, 1745; 1947, **69**, 2942). Partial saponification of the latter with methanolic potassium bicarbonate (Turner, *ibid.*, 1957, **79**, 2271) afforded the required unsaturated cyano-keto-acid (XIa; 70% yield). Reduction of this with lithium and ammonia yielded a gummy product, which on treatment with methanolic hydrogen chloride followed by purification of the product by chromatography on alumina gave methyl 6-*p*-anisyl-3-methoxycarbonyl-2-oxo-3-methylcyclohexane-1-acetate (IIb), m.p. 93° (undepressed on admixture with an authentic sample*), in 34% yield. Reduction of the olefinic bond in this case was quite stereoselective, for only the saturated di-ester (IIb) and not any of its isomers could be isolated.



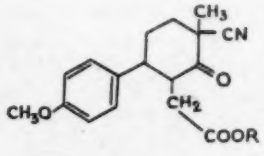
(X)



(XIa): R = H
(XIb): R = CH_3



(XII)



(XIIIa): R = H.
(XIIIb): R = CH_3.

*We are indebted to Professor W. S. Johnson for supplying us an authentic specimen.

A much better yield was, however, obtained when the saturated keto-ester (VIIc) was converted *via* the isoxazole (XII; 63% yield) and the saturated cyano-keto-ester* (XIIIb; 75% yield) to the required keto-diester (IIb; 72% yield). Partial saponification of the cyano-ester (XIIIb) led to the cyano-keto-acid (XIIIa; 75% yield) which could also be converted into the keto-diester (IIb) in about the same yield.

EXPERIMENTAL†

6-p-*Anisyl*-2-*oxocyclohex*-6-*ene*-1-*acetic Acid* (VIa)–To a solution of sodium ethoxide [from sodium (4g.) and ethanol (104 c.c.)] was added diethyl β-oxoadipate (IVa) (38.5 g.) followed by the Mannich base hydrochloride (III, 20 g.). The mixture was cooled (ice-salt) and with good stirring dimethyl sulphate (16 c.c.) was added dropwise over a period of 45 minutes. The mixture was then stirred for 2 hours and allowed to stand overnight at room temperature. Most of the alcohol was removed by distillation under reduced pressure, water (100 c.c.) was added, and the separated oily liquid was taken up in ether-benzene. The solvent was removed and the residue distilled at 120-25°/1mm to recover the diethyl β-oxoadipate (IVa) (*ca.* 17.5 g.). The remaining orange-coloured condensation product (Va) was a thick liquid and weighed *ca.* 31g.

The crude condensation product (Va, 15.5 g.) was refluxed with aqueous KOH (11.5g. in 104 c. c. water) for 4 hours under nitrogen. The resulting homogeneous liquid was cooled, extracted once with ether, and the aqueous layer acidified with HCl (cold, dilute). A brownish gum separated which solidified on standing; yield 9.65 g. (90% based on the hydrochloride). Crystallisation from benzene-petroleum ether (40-60°) furnished thick prismatic crystals, m.p. 136°; the melt after solidification on standing remelted at 146°. λ_{max} 226 mμ (log ϵ 4.02), 289 mμ (log ϵ 4.12); λ_{min} 252 mμ (log ϵ 3.72). (Found: C, 69.31; H, 6.4. Calc. for $C_{13}H_{16}O_4$: C, 69.23; H, 6.15%). Johnson *et al.* (*loc. cit.*) report m. p. 135-37°, Turner (*loc. cit.*) 137-38.5°, and Guha *et al.* (*loc. cit.*) m.p. 137°.

Esterification of the acid (VIa, 2.6 g.) with diazomethane furnished methyl 6-*p*-anisyl-2-oxocyclohex-6-ene-1-acetate (VIi) (2.61 g., 95.2%), m.p. 93°. Johnson *et al.* (*loc. cit.*) report m.p. 93-93.5°, Turner (*loc. cit.*) 91°, and Guha *et al.* (*loc. cit.*) 95-96°.

6-p-*Anisyl*-2-*oxo*-3-*methylcyclohex*-6-*ene*-1-*acetic Acid* (VIb).—Similarly using sodium ethoxide (4 g. of sodium in 104 c.c. of ethanol), diethyl α-methyl-β-oxoadipate (41g.) (IVb), the Mannich base hydrochloride (III, 20 g.), and dimethyl sulphate (16 c.c.) and by carrying out the condensation as above, 30 g. of crude condensation product (Vb) was obtained.

The condensation product (Vb, 15 g.) was refluxed with aqueous KOH (11.3 g. in 103 c.c. water) for 4 hours under nitrogen. Acidification of the cooled aqueous layer afforded a gum which solidified on standing; yield 6.9 g. (61% based on the hydrochloride). Crystallisation from dilute methanol or benzene-petroleum ether (40-60°) gave white needles, m.p. 147°, λ_{max} 225 mμ (log ϵ 4.14), 289 mμ (log ϵ 4.16), λ_{min} 253 mμ (log ϵ 3.70). (Found: C, 70.04; H, 6.77. $C_{16}H_{18}O_4$ requires C, 70.07; H, 6.56%). Guha *et al.* (*loc. cit.*) report m.p. 142-43°.

*This ester has been prepared by a different method by Johnson *et al.* (unpublished results, Fieser and Fieser, "Steroids", p. 500, Reinhold Publishing Corporation, New York, 1959.

†All boiling and melting points are uncorrected. Ultraviolet absorption was recorded on a Beckman quartz spectrophotometer, DU model, using 95% ethanol as solvent. Alumina used was of Brockmann quality.

Esterification of (VIb, 2.74 g.) with dizomethane furnished *methyl* 6-p-*anisyl*-2-*oxo*-3-*methylcyclohex*-6-*ene*-1-*acetate*, b.p. 120-25°/0.02 mm, which crystallised from petroleum ether (60-80°), m.p. 56°, yield 2.7 g. (93.7%). (Found: C, 70.78; H, 7.29. $C_{17}H_{20}O_4$ requires C, 70.83; H, 6.94%). Guha *et al.* (*loc. cit.*) report m.p. 67°.

6-p-*Anisyl*-2-*oxocyclohexane*-1-*acetic Acid* (VIIa).—(*i*) *Lithium-ammonia Reduction.*—In a 2-litre three-necked flask was placed a solution of 6-*p*-anisyl-2-oxocyclohex-6-ene-1-acetic acid (VIa, 3 g.) in dry ether (30 c.c.) and anhydrous liquid ammonia (800 c.c.) was then introduced. To the well-stirred solution lithium (0.24 g.) was added when a blue colour developed and lasted for about 7 minutes. After complete evaporation of the ammonia, water (100 c.c.) was added to the residue and the aqueous solution extracted once with ether. Acidification of the aqueous layer with HCl (cold, dilute) gave a gummy substance which solidified on standing, m.p. 94°, yield 2.5 g. (82%). On crystallisation from benzene-petroleum ether (40-60°), white crystals, m.p. 111°, were obtained. λ_{max} 226 mμ (log ε 3.96), 277 mμ (log ε 3.19), 283.5 mμ (log ε 3.11), λ_{min} 253 mμ (log ε 2.52), 281.5 mμ (log ε 3.09). (Found: C, 68.95; H, 6.93. $C_{15}H_{18}O_4$ requires C, 68.70; H, 6.87%).

(*ii*) *Catalytic Reduction.*—A solution of methyl 6-*p*-anisyl-2-oxocyclohex-6-ene-1-acetate (VIi, 0.3 g.) in ethanol (10 c.c.) was stirred with 100mg. of 10% Pd-C in an atmosphere of hydrogen. After the absorption of hydrogen had ceased, the catalyst was filtered and the ethanol evaporated. The residue was a gum which could not be crystallised. Treatment with a dilute solution of perchloric acid in ethyl acetate (Robins *et al.*, *loc. cit.*) also led to a gummy substance (0.29 g.). It was then refluxed for 2 hours with methanolic KOH (0.12 g. in 6 c.c. methanol) (Robins *et al.*, *loc. cit.*) under nitrogen. Most of the alcohol was removed under reduced pressure and the residue dissolved in water. After extracting the aqueous solution once with ether, it was acidified with HCl (cold, dilute). The resulting gummy solid was taken up in ether and the solvent removed. The residue on crystallisation from benzene-petroleum ether (40-60°) gave the saturated keto-acid (VIIa), m.p. 111°, yield 0.18 g. (63%).

Esterification of VIIa (2.62 g.) with diazomethane gave *methyl* 6-p-*anisyl*-2-*oxocyclohexane*-1-*acetate* (VIIc), b.p. 120-25°/0.02 mm, which was crystallised from petroleum ether (60-80°), m.p. 68°, yield 2.6 g. (94.2%). (Found: C, 70.11; H, 7.59. $C_{16}H_{20}O_4$ requires C, 69.66; H, 7.24%).

6-p-*Anisyl*-2-*oxo*-3-*methylcyclohexane*-1-*acetic Acid* (VIIb).—A solution of 6-*p*-anisyl-2-oxo-3-methylcyclohex-6-ene-1-acetic acid (VIb, 3 g.) in dry ether (30 c.c.) was reduced as before, using lithium (0.23 g.) and anhydrous ammonia (800 c.c.). The blue colour lasted for 10-12 minutes. The saturated keto-acid (VIIb, 2.45 g., 81%) was a white solid, m.p. 132°. On crystallisation from dilute methanol, white crystals were obtained, m.p. 136°. (Found: C, 69.56; H, 7.39. Calc. for $C_{16}H_{20}O_4$: C, 69.56; H, 7.24%). Turner (*loc. cit.*) reports m.p. 135° and Bhattacharya *et al.* (*loc. cit.*) report m. p. 135-37°.

Esterification of the acid (VIIb, 2.76 g.) with diazomethane furnished methyl 6-p-*anisyl*-2-*oxo*-3-*methylcyclohexane*-1-*acetate* (VIId) as a viscous liquid, b.p. 120-25°/0.01 mm, yield 2.69 g. (92.7%). (Found: C, 70. 06; H. 7.72. $C_{17}H_{22}O_4$ requires C, 70.03; H, 7.58%).

Condensation of Methyl 6-p-*Anisyl*-2-*oxocyclohex*-6-*ene*-1-*acetate* (VIi) *with Methyl Oxalate.*—To finely powdered sodium (0.23 g.), suspended in dry ether (10 c.c.), was added methanol (0.32 g.); the mixture was allowed to stand overnight. It was refluxed for 4 hours,

cooled and dimethyl oxalate (1.18 g.) was added. The apparatus was filled with nitrogen and the mixture refluxed for 10 minutes. The flask was then cooled (ice-salt) and a solution of methyl 6-*p*-anisyl-2-oxocyclohex-6-ene-1-acetate (VIi, 1.37 g.) in dry ether (10 c.c.) was added. On keeping overnight at room temperature, the reaction mixture gradually turned yellow and a little brownish-red solid separated. It was cooled (ice-salt) and ice-cold water (10 c.c.) was added. After separation of the aqueous layer, the solvent layer was extracted thrice with 2% ice-cold NaOH solution. The total aqueous layer was once extracted with ether and then acidified with cold 2*N*-HCl. A yellow turbidity appeared at first and on keeping for several hours in the cold, a brownish solid separated. Crystallisation from methanol furnished the glyoxalate (VIII) as a yellow crystalline solid, m. p. 109-10°, yield 1.44 g. (80%). (Found: C, 63.75; H, 5.67. $C_{19}H_{20}O_7$ requires C, 63.33; H, 5.55%).

6-p-*Anisyl*-3-*ethoxycarbonyl*-2-*oxocylohex*-6-*ene*-1-*acetic Acid* (VIc).—The crude condensation product (Va, 15.5 g.), obtained as described earlier, was dissolved in ethanol (10 c.c.) and added to ethanolic NaOEt (1.25 g. of sodium in 60 c.c. of ethanol) (Dreiding *et al.*, *J Amer. Chem. Soc.*, 1955, **77**, 411). The mixture was allowed to stand overnight at room temperature under nitrogen. After acidification with glacial acetic acid, most of the alcohol was removed under reduced pressure on a water bath. Water was added and the mixture extracted with ether-benzene. The organic layer was then repeatedly extracted with saturated sodium bicarbonate solution. The total bicarbonate layer was once extracted with ether and then acidified with HCl cold, dilute). A gummy substance separated out, which solidified on standing. On recrystallisation from benzene-petroleum ether (40-60°), white needles of the acid-ester (VIc) (10 g., 73% based on the hydrochloride), m.p. 106°, were obtained. λ_{max} 225mμ (log ε 4.07), 290 mμ (log ε 4.14), λ_{min} 253 mμ (log ε 3.78). (Found: C, 65.21; H, 6.0. $C_{18}H_{20}O_6$ requires C, 65.06; H, 6.02%).

6-p-*Anisyl*-3-*ethoxycarbonyl*-2-*oxo*-3-*methylcyclohex*-6-*ene*-1-*acetic Acid* (VId).—A solution of the condensation product (Vb, 15. g.) in ethanol (15 c.c.) was added to a solution of sodium ethoxide (1.3 g. of sodium in 45 c.c. ethanol) and the mixture allowed to stand overnight at room temperature under nitrogen. The product was worked up as before to afford a hard gum, b.p. 150-55°/0.012 mm, yield 6.1 g. (43% based on the hydrochloride). (Found: C, 65.52; H, 6.14. $C_{19}H_{22}O_6$ requires C, 65.89; H, 6.35%).

6-p-*Anisyl*-3-*ethoxycarbonyl*-2-*oxocyclohex*-6-*ene*-1-*acetic Acid* (VIe).—A solution of the condensation product (Va, 15.5 g.) in methanol (15 c.c.) was added to a solution of sodium methoxide (1.25 g. of sodium in 45 c.c. of absolute methanol) and by carrying out the experiment as before, the acid-ester (VIe) was obtained as a pale yellow solid, yield 10g. (76% based on hydrochloride). On crystallisation from ethyl acetate, white crystals, m.p. 164°, were obtained. (Found: C, 64.16; H, 5.99. Calc. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66%). Turner (*loc. cit.*) reports m.p. 163-65°, Johnson *et al.* (*loc. cit.*) 168-68.5°, and Guha *et al.* (*loc. cit.*) 168°.

6-p-*Anisyl*-3-*methoxycarbonyl*-2-*oxo*-3-*methylcyclohex*-6-*ene*-1-*acetic Acid* (VIf).—By adding a solution of the condensation product (Vb, 15 g.) in methanol (15 c.c.) to a solution of sodium methoxide (1.3 g. of sodium in 45 c.c. of absolute methanol) and by carrying out the experiment as before, the acid-ester (VIf) was obtained as a pale yellow solid, yield 7.2 g. (61% based on the hydrochloride). It was crystallised from benzene-petroleum ether (40-60°) to afford white needles, m.p. 127°. (Found: C, 65.51; H, 6.03. Calc. for $C_{18}H_{20}O_6$: C, 65.06; H, 6.02%). Johnson *et al.* (*loc. cit.*) report m.p. 129.5-30° and Guha *et al.* (*loc; cit.*) 129°.

Methyl 6-p-*Anisyl*-3-*ethoxycarbonyl*-2-*oxo*-3-*methylcyclohex*-6-*ene*-1-*acetate* (VIg).—The acid-ester (VIc, 3.32 g.), on esterification with diazomethane, furnished *methyl* 6-p-*anisyl*-3-*ethoxycarbonyl*-2-*oxocyclohex*-6-*ene*-1-*acetate*, b.p. 120-25°/0.004 mm, yield 3.3 g. (95.3%). (Found: C, 65.70; H, 6.62. $C_{19}H_{22}O_6$ requires C, 65.89; H, 6.35%).

A solution of the aforementioned ester (1.56 g.) in benzene (5 c.c.) was dropped into a suspension of sodium hydride (125 mg.) in benzene (20 c.c.) under nitrogen and refluxed for 4 hours on a water bath, when all the sodium hydride disappeared, forming a pale red solution. The reaction mixture was cooled, methyl iodide (4 c.c.) added, and the mixture was allowed to stand at room temperature for 2 hours. After refluxing for 2 hours, a further quantity of methyl iodide (2 c.c.) was added and the refluxing continued for another 2 hours. To the cooled product ice-cold water was added, the benzene layer separated, and the aqueous layer extracted once with ether. The total organic layer was once washed with water and the solvent removed. The residue was purified by short-path distillation, b. p. 135-40°/0.005 mm; yield of the methylated product (VIg) was 1.44 g. (89%). (Found: C, 66.43; H, 6.57. $C_{20}H_{24}O_6$ requires C, 66.66; H, 6.6%).

The same di-ester (VIg) could also be obtained by esterification of the acid-ester (VId).

Lithium-ammonia Reduction of 6-p-*Anisyl*-3-*ethoxycarbonyl*-2-*oxocyclohex*-6-*ene*-1-*acetic Acid* (VI c).—The acid-ester (VIc, 1.15 g.), dissolved in a mixture of dioxan (6 c.c.) and ether (6 c.c.), was reduced with anhydrous liquid ammonia (400 c.c.) and lithium (0.07 g.). The product (0.9 g.) was esterified with diazomethane and the resulting di-ester (0.8 g.) chromatographed over alumina (24 g.) to yield the following fractions: (*i*) petroleum ether (40-60°)-benzene (3:1), 0.133 g.; (*ii*) benzene-ether (2:1), 0.432 g.; (*iii*) ether-methanol (3%), 0.145 g.

The fraction (*i*) solidified on standing. It melted at 68° after one crystallisation from petroleum ether (60-80°) and did not depress the m.p. of methyl 6-*p*-anisyl-2-oxocyclohexane-1-acetate (VIIc). The fraction (*ii*) was a viscous oil, b.p. 120-25°/0.004 mm; λ_{max} 226 mμ (log ε 3.98), 290 mμ (log ε 3.96), λ_{min} 253 (log ε 3.61). On treatment of this substance (0.155 g.) with refluxing 5% aqueous KOH (4 c.c.), the known 6-*p*-anisyl-2-oxocyclohex-6-ene-1-acetic acid (VIa, 0.088 g.), m.p. 136° (after crystallisation), was obtained.

Fraction (*iii*) was purified by short-path distillation, b.p. 125-30°/0.003 mm; λ_{max} 226 mμ (log ε 4.02), 277 mμ. (log ε 3.23), 283 mμ (log ε. 3.25), λ_{min} 264 mμ (log ε 2.56), 281.5. mμ (log ε. 3.15). The compound did not furnish a solid product on treatment with 5% aqueous alkali.

Lithium-ammonia Reduction of 6-p-*Anisyl*-3-*methoxycarbonyl*-2-*oxo*-3-*methylcyclohex*-6-*ene*-1-*acetic Acid* (VIf).—Reduction of the acid-ester (VIf, 1.0 g.) using anhydrous liquid ammonia (500 c.c.) and lithium (0.063 g.) afforded 0.82 g. of a product, which was esterified with dizomethane. The resulting ester (0.75 g.) was chromatographed over alumina (24 g.) and three fractions were collected: (*i*) petroleum ether (40-60°)-benzene (2:1), 0.155g.; (*ii*) benzene-ether (1:1), 0.322 g.; (*iii*) ether-methanol (3%), 0.121 g.

The fraction (*i*) (0.15 g.) was rechromatographed over alumina (4.5 g.) when the bulk of the material (0.122 g.) was eluted with petroleum ether (40-60°)-benzene (3:1). It is a viscous liquid, b.p. 120-25°/0.02 mm. λ_{max} 226 mμ (log ε 4.079), 277 mμ (log ε 3.27), 283 mμ (log ε 3.19), λ_{min} 252 mμ (log ε 2.51), 281.5 mμ (log ε 3.08). (Found: C, 70.48;

H, 7.14. Calc. for $C_{17}H_{22}O_4$: C, 70.03; H, 7.58%). Hydrolysis of 0.102 g. of the substance by refluxing with 5% aqueous KOH (2.5 c.c.) under nitrogen afforded the known 6-*p*-anisyl-2-oxo 3-methylcyclohexane-1-acetic acid (VIIb, 0.063 g.), which on crystallisation from benzene-pertloleum ether (40-60°) melted at 136°. On rechromatography of the fraction (*ii*) (0.32 g.) over alumina (12 g.), most of the material (0.3 g.) was eluted with benzene-ether (1:1) and distilled at 122-27°/0.01 mm. λ_{max} 226 mμ (log ε 4.06), 289 mμ (log ε 4.0), λ_{min} 255 mμ (log ε 3.71). On treatment of the substance (0.155 g.) with refluxing 5% aqueous alkali (4 c.c.), it afforded the known 6-*p*-anisyl-2-oxo-3-methylcyclohex-6-ene-1-acetic acid (VIb, 0.092 g.) which after one crystallisation from benzene-petroleum ether (40-60°) melted at 146°.

The fraction (*iii*) (0.121g.) was rechromatographed over alumina (4 g.) when most of it (0.102 g.) was eluted with ether methanol (3%), b.p. 125-30°/0.02 mm. λ_{max} 227 mμ (log ε 4.04), 277 mμ (log ε 3.26), 283 mμ (log ε 3.23), λ_{min} 253 mμ (log ε 2.58), 281.5 mμ (log ε 3.24). (Found: C, 67.56; H, 8.39. $C_{18}H_{26}O_5$ requires C, 67.08; H, 8.07%). On the basis of U.V. data and analysis, the product was presumed to be (IXb).

Methyl 6-p-*Anisyl*-4, 5-*dihydrobenz*-(2, 1-d)*isoxazole*-7-*acetate* (X).— To a cooled suspension of sodium methoxide (from 0.3 g. of sodium and 0.415 g. of methanol) in thiophene-free benzene (25 c.c.) was added ethyl formate (2.5 c.c.) and the air in the apparatus was replaced by nitrogen. After 30 minutes, a solution of the ester (VIi, 1.6 g.) in benzene (5 c.c.) was slowly dropped with stirring. Stirring was continued for 2 hours and the reaction mixture allowed to stand at room temperature overnight. The flask was cooled (ice-water), ice-cold water added, and thoroughly shaken. The aqueous layer was separated and the organic layer repeatedly extracted with 2% ice-cold NaOH solution. The total aqueous layer was once extracted with ether and then acidified with HCl (cold, dilute). The resulting yellow gummy product was taken up in ether-benzene, washed with ice-cold water, and the solvent removed. The yield of the crude hydroxymethylene derivative, which gave a violet colour with ethanolic ferric chloride, amounted to 1.7 g. It could not be crystallised.

A solution of the crude hydroxymethylene derivative (1.7 g.) in glacial acetic acid (20 c.c.) was stirred for 8 hours at 70-80° with dry powdered hydroxylamine hydrochloride (0.6 g.). Most of the acetic acid was removed under reduced pressure on a water bath, the residue diluted with water, and extracted with ether-benzene. The organic layer was washed with 5% sodium bicarbonate solution followed by water. Removal of the solvent gave a gummy substance, b.p. 145-50°/0.005 mm, yield 0.65 g. (37%). Crystallisation from dilute methanol gave pale yellow plates, m.p. 77-79°. (Found: N, 4.50. $C_{17}H_{17}O_4N$ requires N, 4.68%).

Methyl 6-p-*Anisyl*-3-*cyano*-2-*oxo*-3-*methylcyclohex*-6-*ene*-1-*acetate* (XIb).— A solution of the isoxazole (X, 0.55 g.) in dry butanol[t] (5 c.c.) was added to potassium butoxide[t] in butanol[t] (0.22 g. of potassium in 6 c.c. of butanol[t]) and the mixture refluxed for 15 minutes. It was then cooled, methyl iodide (3 c.c.) was added, and left at room temperature for 1 hour with frequent swirling. More methyl iodide (2 c.c.) was added and the mixture refluxed for 4 hours. After removal of the alcohol under reduced pressure, the residue was treated with water and ether-benzene. The organic layer was washed with water and the solvent removed. The product (XIb), b.p. 130-35°/0.005 mm, weighed 0.525 g. (91%). (Found: C, 69.39; H, 5.95; N, 4.89. $C_{18}H_{19}O_4N$ requires C, 69.01; H, 6.07; N, 4.47%).

6-p-*Anisyl*-3-*cyano*-2-*oxo*-3-*methylcyclohex*-6-*ene*-1-*acetic Acid* (XIa).—To a solution of the cyano-ester (XIb, 0.525 g.) in methanol (15 c.c.) was added aqueous potassium bicarbonate (1 g. in 3 c.c. water). After 2 hours of refluxing, the mixture was evaporated in vacuum and the residue treated with water. The aqueous solution was once extracted with ether and then acidified with HCl (cold, dilute) to yield a gummy acid which was taken up in ether. After removal of the solvent, the residue was crystallised from benzene-petroleum ether (40-60°) to yield 0.35 g. (70%) of the unsaturated cyano-keto-acid (XIa), m.p. 126. λ_{max} 225 mμ (log ε 4.03), 298 mμ (log ε 4.07), λ_{min} 256 mμ (log ε 3.65). (Found: C, 67.98; H, 5.11; N, 5.04. $C_{17}H_{17}O_4N$ requires C, 68.22; H, 5.68; N, 4.68%).

Methyl 6-p-*Anisyl*-4,5,6,7-*tetrahydrobenz*-(2,1-d)*isoxazole*-7-*acetate* (XII).—Using sodium methoxide (0.28 g. of sodium and 0.385 g. of methanol), ethyl formate (1.6 c.c.), saturated methyl ester (VIIc; 1.42 g.), and benzene (25 cc.) the corresponding hydroxymethylene derivative (1.5 g.) was obtained by carrying out the experiment as described before. In this case also the hydroxymethylene derivative could not be crystallised, and it gave a violet colour with ethanolic ferric chloride.

A solution of the foregoing crude hydroxymethylene derivative (1.5 g.) in glacial acetic acid (30 c.c.) was mixed with dry hydroxylamine hydrochloride (0.55 g.) and quickly heated to boiling (about 3 minutes) in an oil bath maintained at 170°. It was refluxed at that temperature for 10 minutes, cooled, and the product worked up as before. It was purified by short-path distillation, b.p. 145-50°/0.006 mm, yield 0.975 g. (63%). λ_{max} 227 mμ (log ε 4.02), 277 mμ (log ε 3.38), 283 mμ (log ε 3.35). λ_{min} 255 mμ (log ε 3.01), 281 mμ (log ε 3.31). (Found: N, 4.45. $C_{17}H_{19}O_4N$ requires N, 4.65%).

Methyl 6-p-*Anisyl*-3-*cyano*-2-*oxo*-3-*methylcyclohexan*-1-*acetate* (XIIIb).—This was prepared in a similar way as (XIb). Using potassium butoxide[t] in butanol[t] (0.22 g. of potassium in 6 c.c. of butanol[t]), isoxazole (XII, 0.55 g.), and methyl iodide (5 c.c.) the gummy methylcyano-ester (XIIIb, 0.515 g.) was obtained. Crystallisation from benzene-petroleum ether (40-60°) gave 0.432 g. (75%) of the pure product as white needles, which melted either at 112° or at 122°. The polymorphism was proved by melting the 112° isomer and seeding the melt at 114° with the 122° isomer when the melt solidified and remelted at 122°. λ_{max} 228 mμ (log ε 3.93), 277 mμ, (log ε 3.23), 283 mμ (log ε 3.16), λ_{min} 256 mμ (log ε 2.76), 281 mμ (log ε 3.12). (Found: C, 68.34; H, 7.09; N, 4.58. $C_{18}H_{21}O_4N$ requires C, 68.57; H, 6.66; N, 4.44%).

6-p-*Anisyl*-3-*cyano*-2-*oxo*-3-*methylcyclohexane*-1-*acetic Acid* (XIIIa).—A solution of the saturated cyano-ester (XIIIb, 0.4 g.) in methanol (12 c.c.) was refluxed with an aqueous solution of potassium bicarbonate (0.8 g. in 2.5 c.c. of water) for 2 hours and the product was worked up as described for the preparation of (XIa). On crystallisation from benzene-petroleum ether (40-60°), white needles of the acid (XIIIa), m.p. 145°, were obtained, yield 0.288 g. (75%). (Found: C, 68.21: H, 6.48; N, 4.87. $C_{17}H_{19}O_4N$ requires C, 67.77; H, 6.31; N, 4.65%).

Methyl 6-p-*Anisyl*-3-*methoxycarbonyl*-2-*oxo*-3-*methylcyclohexane*-1-*acetate* (IIb): (*a*). *From the Unsaturated Cyano-keto-acid* (XIa).—A solution of the unsaturated cyanoketo-acid (XIa; 0.3 g.) in dry ether (10 c.c.) was reduced with lithium (0.021 g.) in anhydrous liquid ammonia (200 c.c.) in the usual way. The crude product (0.225 g.) was dissolved in absolute methanol (6 c.c.) and saturated with dry HCl below 0°, and left at 0° for 3 days. It was then poured into ice-cold water (100 c.c.) and extracted with ether-benzene. After washing the organic layer with 5% sodium bicarbonate solution and water, the solvent was

removed and the residue chromatographed over alumina. On elution with petroleum ether (40-60°)-benzene (1:1), the crystalline di-ester (IIb), m.p. 91°, yield 0.12 g. (34%), was obtained. On crystallisation from petroleum ether (60-80°), it gave white needles, m.p. 93°, undepressed on admixture with an authentic sample. λ_{max} 226 mμ (log ε 3.98), 277 mμ) (log ε 3.23) 283 mμ (log ε 3.17), λ_{min} 276 mμ (log ε 2.76), 281 mμ (log ε 3.11). (Found: C, 65.45; H, 6.7. Calc. for $C_{19}H_{24}O_6$: C, 65.51; H, 6.89%).

(*b*). *From the Saturated Cyano-keto-ester* (XXIIIb).— A solution of the pure cyano-ester (XIIIb, 0.432 g., m.p. 112°) in absolute methanol (8 c.c.) was treated with dry HCl as before. After working up in the usual manner, the gummy product was triturated with petroleum ether (40-60°) for a long time (yield of the keto-diester has been found to suffer if sufficient time is not allowed for solidification), and the crude material was recrystallised from dilute methanol or petroleum ether (60-80°) to yield 0.344 g. (72%) of the keto-diester (IIb), m.p. 93°.

When the crude gummy cyano-keto-ester (XIIIb, 0.515 g.) without further purification was similarly treated with dry HCl gas, the saturated keto-diester (IIb, 0.349 g.), m.p. 93°, was obtained.

(*c*) *From the Saturated Cyano-keto-acid* (XIIIa).—A methanolic solution of the cyano-keto-acid (XIIIa, 0.15 g.) in absolute methanol (5 c.c.), on treatment with dry hydrogen chloride, as described earlier, furnished the keto-diester (IIb), m.p. 93°, yield 0.124 g. (71%).

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Electrochemistry of Fluoride Solutions. Part VI. Electrodeposition of Nickel from Fluoride Solutions

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The electrodeposition of nickel from acid fluoride solutions has been studied. The decomposition, discharge, and anodic dissolution potentials of Ni in acid baths have been determined. Nickel dissolves continuously at the anode without any signs of passivity. The nature of the deposits from different solution and the effect of addition agents on deposits have been studied. Hydrogen peroxide proved to be the best addition agent in acid fluoride solutions. The operating conditions for the acid fluoride bath with hydrogen peroxide as the addition agent have been specified. This bath, which yields much better deposits than any other acid bath, deserves a high place in the list of nickel plating baths.

Marino (B.P. 2316/1912) patented the use of fluoride and fluoride-tartrate solutions for depositing nickel on aluminium by immersion, aided by an electric current. Smith (*Trans. Electrochem. Soc.*, 1915, **27**, 28) reported the electrolytic separation of cobalt from nickel in ammoniacal fluoride solution. Strong ammoniacal fluoride solutions were also employed by Edmister and Cooper (*J. Amer. Chem Soc.*, 1920, **42**, 2419) for estimating nickel electrolytically. Brown (U. S. P. 2,550,449/1951) took out a patent to cover the use of fluoride solutions containing boric acid and organic brightners for depositing nickel. These are the only references to be found in literature on the electrolytic use of nickel fluoride solutions. The electrochemistry of nickel fluoride thus appears to have been neglected and no coherent and systematic data are available to enable us to form a definite view about the suitability of nickel fluoride for nickel plating. The present investigation was undertaken to obtain the required information.

The normal fluoride of nickel is only slightly soluble in water, but the solubility is reasonably good in solutions of hydrofluoric acid. The present investigation has therefore been carried out with acid fluoride baths and data obtained on (*a*) decomposition and discharge potentials of acid nickel fluoride as well as the dissolution potential of nickel in the same solution, (*b*) nature of cathodic deposits from neutral and acid fluoride baths with and without the addition of inorganic and organic agents, and (*c*) porosity of different deposits obtained under different conditions.

EXPERIMENTAL

Nickel Fluoride Solutions

Acid Solutions.—The precautions and experimental technique in dealing with fluoride and acid fluoride solutions have been detailed in the earlier publications in this series.

Nickel carbonate (C. P.) was added to hydrofluoric acid until a precipitate just began to appear (Mellor, "Comprehensive Treatise on Inorganic and Theoretical Chemistry", 1936, Vol. 15, p. 402; Edmister and Cooper, *loc. cit.*). The precipitate was filtered and the filtrate used for experiments.

Neutral Solutions.—The addition of nickel carbonate to hydrofluoric acid was continued even after the appearance of a precipitate until effervescence had completely ceased. The insoluble matter at this stage was filtered and the neutral filtrate was used whenever required.

Analysis.—The estimation of nickel was made by the cyanide method. Preliminary experiments with mixtures of known amount of nickel sulphate and hydrofluoric acid containing $HF/NiSO_4$ ratios up to 37 showed that the method was capable of providing accurate results with acid fluoride solutions. The details and precautions enumerated by Mellor and Thomson ("A Treatise on Quantitative Inoraganic Analysis", 1938) were strictly adhered to and the cyanide solution was standardised against recrystallised Merck's C.P. grade nickel ammonium sulphate.

The amount of hydrofluoric acid remaining unneutralised in the acid solutions was calculated by difference. The quantity of free hydrofluoric acid was always so great in proportion to NiF_2 that the measurement of *p*H was not made as being of no particular significance.

Porosity Tests.—The porosity of nickel plates on copper specimens was tested by the ferroxyl test using potassium ferrocyanide instead of the usual ferricyanide. The porous spots are indicated by red coloured spots.

DISCUSSION OF RESULTS

Potential Measurements

The potential measurements are summarised in Table I. The discharge potential measurements were made with reference to a saturated calomel electrode and the values reduced to the hydrogen scale.

TABLE I

Solution composition.	Decomposition potential.		Discharge potentials.			Dissolution potential of nickel.	
	1st break.	2nd break	Anode.	Cathode 1st break.	Cathode 2nd break.	1st break.	2nd break.
1. 0.3214*M*-NiF_2 0.6806*M*-HF	1.68	2.17	1.73	0.05	-0.35		
2. 0.2280*M*-NiF_2 0.4960*M*-HF	1.67	2.18	1.71	0.04	-0.36		
3. 0.1205*M*-NiF_2 0.2575*M*-HF	1.71	2.17	1.74	0.03	-0.40	0.07	2.65
4. 0.2280*M*-NiF_2 0.4960*M*-HF 0.2820g./litre H_2O_2	0.84	1.27	0.86	0.02	-0.26		

The first decomposition potential and the first break in the cathode current-potential curve are, as observed earlier by Talaty (this *Journal*, 1952, **29**, 149). due to the discharge of the trace impurity copper in the hydrofluoric acid. This disappears after the first few minutes of electrolysis.

The discharge potentials of nickel (in the range of -0.35 to -0.40 volt depending on the concentration of nickel) are much more negative than what should be expected from a consideration of the normal electrode potential of the metal (-0.23 volt on the hydrogen scale) and the concentrations of nickel salt in the solutions. Much greater discrepancies have been known in the deposition of nickel, iron, and cobalt from solutions of their sulphates at room temperatures. Further, it is also known that chlorides and other halides reduce the magnitude of this discrepancy and cause the metals to be deposited at values much closer to the reversible values. No satisfactory explanation of this phenomenon has been advanced, but it is clear that irreversibility of some sort and interference with the usual processes of ion discharge and metal deposition are present in these cases. What is more interesting and relevant to the present case, however, is the greater proximity of the cathode discharge potentials to the reversible values in fluoride solutions than in sulphate baths and this itself is a point in favour of the fluoride baths. The dissolution potential of nickel in a solution (0.1205*M*-NiF_2 and 0.2575*M*-HF) was measured. Two breaks, the lst at 0.07 and the 2nd at 2.65, were observed in the current anode potential curve (Fig. 1). That the first is the dissolution potential of Ni whereas the second corresponds to oxygen discharge was established by actual experiment. What is noteworthy here, however, is the fact that the nickel anode continued to dissolve even at higher potentials in spite of the evolution of oxygen, without any exhibition of passivity—a phenomenon quite so different from what is found in sulphate solutions.

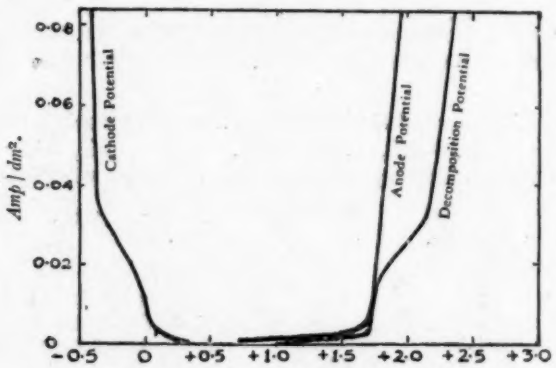

FIG. 1 0.2280*M*-NiF_2,0.4960*M*-HF.29°.

Electrodeposition of the Metal

The experiments were all carried out at room temperature (29-30°) with agitation of the electrolyte. The anode consisted of a plate of pure nickel. Initially deposits were obtained on platinum cathodes and later on copper cathodes. For all tests the deposition was continued usually for one hour.

Neutral fluoride solutions proved unsatisfactory, the deposits obtained being dark and non-adherent. The addition of neutral sodium and potassium fluorides did not improve deposits very much. Acid fluoride solutions proved more effective. The deposits were compact and solid, fine grained but rather dull in colour in concentrated solutions. Acid fluoride solutions at comparatively low dilutions gave much better deposits. The deposits were sufficiently lustrous and adherent, but at reasonable current densities there was a tendency for the deposits to grow 'trees' or 'whiskers' at the edges of the plates.

The most favourable concentrations for the acid fluoride bath were found to be 0.2280*M*-NiF_2 and 0.4960*M*-HF. Except, where otherwise stated, trials were always conducted with a cathodic current density of 4.0 amp./dm^2.

The addition of small quantities of ammonium fluoride to the acid bath improved the cathode current efficiency as well as the nature of the deposit; when the addition was above 0.5 g./litre, the deposit deteriorated. The maximum current efficiency observed at the cathode was 80% when the cathode current density employed was 4 amp./dm^2. The anode current efficiency was invariably higher than 100% in acid baths, indicating that free hydrofluoric acid present in the baths had considerable corrosive effect on a nickel surface, freshly formed by anodic dissolution.

Influence of Addition Agents

The following addition agents were investigated: (1) peptone, (2) thiourea, (3) naphthalene-β-sulphonic acid, (4) glucose, (5) gelatine, (6) gelatine + naphthalene-β-sulphonic acid, (7) brucine, (8) hydrogen peroxide. Almost all of these improved the appearance of the deposit to some extent, glucose, gelatine, and hydrogen peroxide being the most effective even when small quantities were added.

Hydrogen peroxide proved to be the best agent for obtaining smooth deposits while maintaining good cathode efficiency. The deposits were good, entirely free from pits, quite lustrous, and nonporous. The optimum concentration by hydrogen peroxide was determined to be 0.2820 g./litre in the bath. Further increase in the concentration of this addition agent rendered the deposit duller and somewhat brittle. The nature of the deposit and other conditions are detailed in Table II.

TABLE II

Influence of the addition of hydrogen peroxide.

Solution = 0.2280*M*-NiF_2 - 0.4960N.HF. Current density = 4.0 amp./dm^2.

Cathode: Copper, except when mentioned otherwise.

No.	Hydrogen peroxide (g./litre).	Applied voltage.	Cathode efficiency.	Nature of deposit.
1.	0.0202	2.65	65.23	Deposit much smoother and brighter than without addition agent.
2.	0.0404	2.55	68.52	Deposit much better than in (1).
3.	0.1010	2.55	67.42	Same as in (2).
4.	0.1614	2.50	67.82	Better than in (3).
5.	0.2017	2.40	69.16	Ductile, lustrous and fine.
6.	0.2820	2.30	70.53	Lustrous, ductile, fine-grained, and smooth. The deposit took on a very high polish on buffing more easily than in any previous case.
7.	0.3800	2.25	69.82	About the same as in (6).
8.	0.6802	2.35	63.02	Deposit became somewhat brittle and edges of the plate were thicker and rougher.

Data in Table II indicate the excellence of the acid fluoride bath when hydrogen peroxide is used with the addition agent (the optimum concentration being 0.2820 g./litre).

The figures recorded in the last horizontal row of Table I point to the further advantage of this bath in that the addition of hydrogen peroxide lowers the decomposition potential very considerably, thus reducing the voltage to be applied for maintaining any given current density. Figs. 2 and 3 (A and B) indicate two causes for the lowering of the decomposition potential. Firstly, hydrogen peroxide exerts a depolarising effect at the cathode and the cathode discharge potential is brought much nearer to the reversible potential (differing from

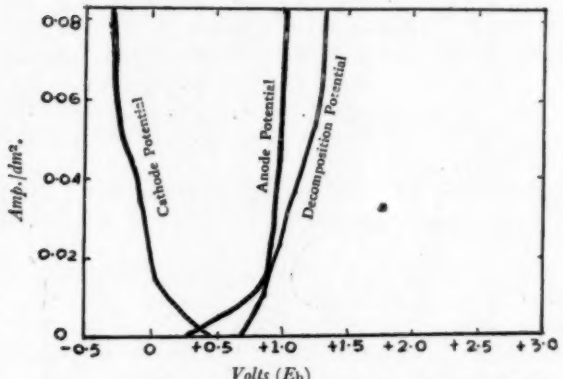

FIG. 2. 0·2280*M*-NiF_2, 0·4960*M*HF;H_2O_2, 0·2820 g/L 29°.

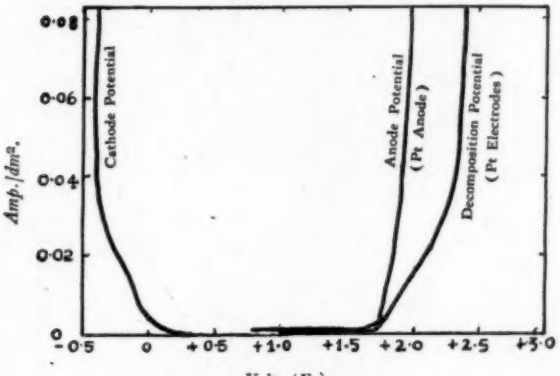

FIG. 3A. 0·1205*M* NiF_2, 0·2575*M* HF. 29°C.

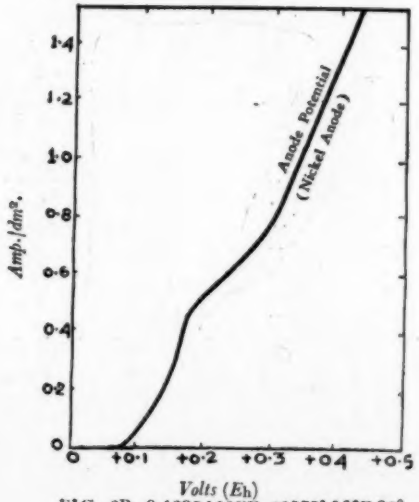

FIG. 3B. 0·1295*M* NiF. 02575M HF.29°.

the latter only by 0.02 volt). Such proximity is rather unusual for a metal like nickel and thus constitutes a great advantage of this bath over all other baths for nickel plating. Secondly, the presence of hydrogen peroxide has lowered anode polarisation and potential. The value for anode discharge potential found here (0.86 volt) is very nearly the same as the one found by Hickling and Wilson (*J. Electrochem. Soc.*, 1951, **98**, 425) for anodic discharge potential for hydrogen peroxide solutions (0.84-8.70 volt) in sulphuric acid over a wide range of concentrations.

It was felt important to determine the rate of disappearance of hydrogen peroxide from the bath, in the light of the inference in the previous paragraph. It was found very surprising that less than 1/3 of the toal peroxide had disappeared in the course of continuous electrolysis for twelve hours and it was found that replenishment to the required extent once in twelve hours was quite adequate to run the bath continuously.

Cathode current efficiency has been indicated in Table II and it is quite as good as may be expected in an acid bath.

Porosity of Deposits

Typical deposits on copper electrodes from different baths were subjected to porosity tests. In all cases, the deposits were obtained by electrolysis for a period of one hour at a current density of 4 amp./dm^2.

TABLE III

Acid fluoride baths.

No.	Substance added.	Remarks.
1.	No addition agent	Non-porous
2.	Am. fluroide	,,
3.	Sod. fluoride	,,
4.	Sod. carbonate	,,
5.	Pot. carbonate	,,
6.	Peptone	Very porous
7.	Brucine	,,
8.	Gelatine	,,
9.	Napththalene sulphonic acid	Non-porous
10.	Glucose	,,
11.	Hydrogen peroxide	,,

It would thus be seen that in most cases the deposit is non-porous. The operating conditions of the bath giving the best results are recorded in Table IV.

TABLE IV

Solution composition	..	0.2280*M*-NiF_2, 0.4960*M*-HF; H_2O_2, 0.2820 g./litre.)
Cathode current density	..	4.0 amp./dm^2., with agitation of the electrolyte.
Anode current density	..	2.0 amp./dm^2
Applied potential	..	2.3 volts
Temperature	..	29°
Cathode current efficiency	..	70.53%
Anode current efficiency	..	104.53%

From this study, it is concluded that the best fluoride bath, described above, deserves recognition for a high place in the list of good, low-*p*H nickel-plating baths.

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Syntheses of Furano Compounds. Part XIX. Analogues of Homopterocarpin and Related Compounds

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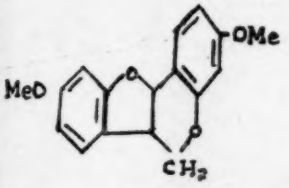
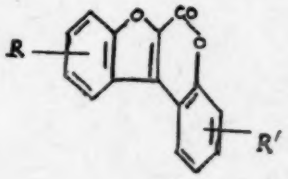
Chromeno-(3′, 4′-2, 3)-coumarones have been synthesised from the related coumarins and then catalytically reduced to chromano-(3′, 4′-2,3)-coumarans having a *cis* junction.

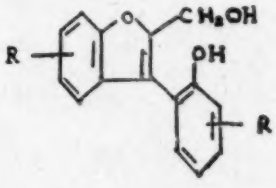
In this paper are described our experiments to synthesise chromano-(3′,4′-2,3)-coumarans of the type (V) which bear close resemblance to chromano-(3′,4′-2,2)-coumaran, the latter forming the ring structure of homopterocarpin (I) or pterocarpin of established constitution (McGookin *et al.*, *J. Chem. Soc.*, 1940, 787; Späth and Schlager, *Ber.*, 1940, **73**, 1; Robertson and Whalley, *J. Chem. Soc.*, 1954, 1440). Such a synthesis was obviously desirable not only in the interest of preparing analogues of homopterocarpin but also for securing products with known stereochemical disposition at the junction of the reduced rings because the nature of ring-fusion in the pterocarpins is still undefined.



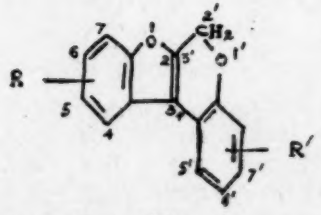
(I)



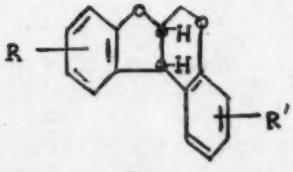
(II)



(III)



(IV)

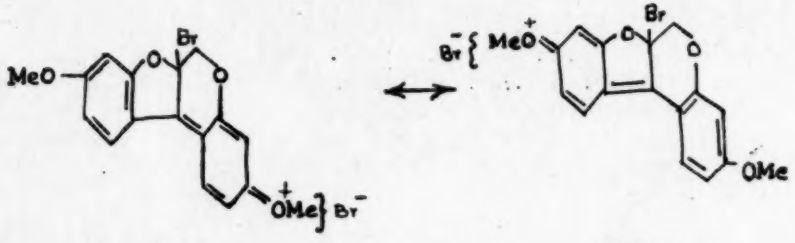


(V)

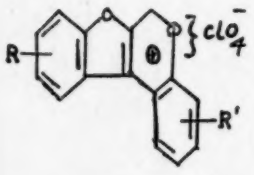
The chromano-coumarans have been synthesised from coumarino-(3′, 4′-2,3)-coumarones (II), the latter having been synthesised by King *et al.* (*J. Chem. Soc.*, 1948, 1672) by von Pechmann's method by the condensation of *m*-dihydroxyphenols and ethyl *β*-coumaranone-2-carboxylates. On reduction with lithium aluminium hydride the lactone group of (II) was smoothly reduced to the phenolic alcohol (III), the furan ring remaining unaffected in the reduction. This is in contrast to the reduction of coumarino-(3′, 4′-3,2)-coumarones in which the simultaneous hydrogenation of the furan ring takes place (Chat-

terjea and Dhoubhadel, unpublished results). The cyclisation of (III) by phosphorus tribromide and subsequent treatment with alkali (cf. Benneville and Connor, *J. Amer. Chem. Soc.*, 1942, **62**, 883) was unsuccessful on account of extensive formation of polymeric products, whereas attempted cyclisation with sodium acetate—acetic anhydride led only to the formation of a diacetate. The desired cyclisation however, took place when a solution of the phenolic alcohol in diethylene glycol was boiled, the period of boiling being sometimes critical. By this method a fairly consistent yield of 7′-methoxy-, 5′,7′-dimethoxy-, 6,7′-dimethoxy-, and 6,5′,7′-trimethoxy-chromeno-(3′,4′-2,-3)-coumarcnes were obtained.

6,7′- Dimethoxychromeno-(3′,4′-2,3)-coumarone (IV:R=R′=OMe at 6 and 7′) is related to dehydrohomopterocarpin. In common with all the chromenes of this series, this compound was converted into the corresponding pyrylium salt (structure VII) on treatment with triphenylmethyl perchlorate (cf. Bonthrone and Reid, *J. Chem. Soc.*, 1959, 2773; Chatterjea and Mukherjee, *Experientia*, 1960, **16**, 439); the compound was also readily



(VIA) (VIB)



(VII)

oxidised by ferric chloride in acetic acid to the related pyrylium ferrichloride. On treatment with bromine vapour in acetic acid, a crimson solution was obtained with the separation of a crystalline deep red product. This is undoubtedly due to the formation of the quinonoid dibromide (VIA or VIB), in which both the resorcinol nuclei become partly quinonoid. The compound loses hydrogen bromide very slowly and passes into the pyrylium salt. This change may be brought about quickly in presence of acetone. This behaviour is also shown by 6,5′,7′-trimethoxychromeno-(3′,4′-2,3)-coumarone, in which the methoxyl groups of the resocinol and phloroglucinol nuclei are in conjugation. On the other hand, 7′-methoxychromeno- and 5′, 7′- dimethoxychromenocoumarones gave a transient coloration with bromine with the ready separation of the pyrylium bromides. The formation of a dibromide, mentioned above, recalls the behaviour of deoxythrimetylbrazilone (Perkin *et al.*, *J. Chem. Soc.*, 1928, 1504) which also forms an unstable dibromide and passes into trimethoxybrazilium salt.

The chromenes described above are smoothly reduced by palladised charcoal in acetic acid to *cis*-chromano-(3′, 4′-2,3)-coumarans (V) and as these products do not contain any benzyloxy linkage, further hydrogenolysis is not possible as in the case of the pterocarpins (cf. McGookin *et al.*, *loc. cit.*). The ultraviolet absorption spectrum of the chroman (V: R=R′=OMe at 6 and 7′) is very similar to that of homopterocarpin and different from that of its ring-fusion isomeride (isohomopterocarpin). Although this signifies that the former may have a *cis* junction, further direct experimental evidence is necessary to establish the point. Work in this direction is in progress.

EXPERIMENTAL

All m.p's are uncorrected. The ultraviolet absorption spectra were taken in ethanol solution and measured in a Beckman quartz spectrophotometer. Several analyses of pyrylium perchlorates could not be carried out due to explosion in the combustion tube.

Ethyl 6-Methoxy-β-coumaranone-2-carboxylate.—A solution of ethyl 5-methoxy-2-ethoxycarbonylphenoxyacetate (16.0 g.) in dry purified benzene (150 c.c.) was added to powdered sodium (1.28 g.) and the mixture refluxed gently for 2 hours on a water bath. The sodium salt separating was dissolved in sufficient water and the aqueous layer was acidified to afford the crude ester (10 g.) which crystallised from petroleum ether in colorless plates (9.5g.), m.p. 117° (King *et al.* report m.p. 112°), showing a green ferric reaction in ethanol. (Found: C, 61.1; H, 5.1. Calc. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1%).

2-Hydroxymethyl-3-(2-hydroxy-4-methoxyphenyl)-coumarone.—A suspension of 7-methoxycoumarono-(2′,3′,-3,4)-coumarin (King *et al.*, *loc. cit.*) (1. 8. g.) in dry ether (50 c.c.) was stirred at the room temperature for 2 hours with lithium aluminium hydride (0.4 g.) with proper exclusion of atmospheric moisture and then left overnight. The mixture was carefully decomposed with H_2SO_4(dil.) and the ethereal solution on working up yielded a viscous liquid, which solidified when rubbed with benzene. On crystallisation from benzene the *hydroxymethyl compound* (1.2 g.) was obtained in colorless prisms, m.p. 106° (evolution of gas at 170-90°). (Found: C, 70.9; H, 5.1. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%). The *diacetyl derivative*, prepared by heating with sodium acetate and acetic anhydride, crystallised from ethanol in colorless needles, m.p. 130°. (Found: C, 67.6; H, 5.2. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%).

2-Hydroxymethyl-3-(2-hydroxy-4,6-methoxyphenyl)-coumarone was similarly prepared from 5,7- dimethoxycoumarono-2′, 3′-?, 4)-coumarin and obtained in colorless prisms, m.p. 112° from benzene; yield 80%. (Found: C, 68.0; H, 5.6. $C_{17}H_{15}O_5$ requires C, 68.0; H, 5.3 %). λ_{infl} 237-39 mμ (log ε 4.0) and 260-62mμ (log ε 3.7). The *diacetate* crystallised from ethanol in colorless plates, m.p. 108°, depressed to 96° on admixture with the original diol. (Found: C, 65.7; H, 5.2. $C_{21}H_{20}O_7$ requires C, 65.6; H, 5.2%).

2-Hydroxymethyl-3-(2-hydroxy-4-methopxyhenyl)-6-methoxycoumarone.–6,7′-Dimethoxycoumarono-(2′,3′-3,4)-coumarin (m.p. 226°) (1.0 g.) was dissolved in excess of dry ether (400 c.c.) and added to an excess of lithium aluminium hydride (0.8 g.) in ether (50 c.c.); the mixture was stirred at the room temperature for 3 hours. On working up in the usual manner, the *hydroxymethyl compound* (0. 8g.) separated from benzene in reddish prisms, m.p. 150°. (Found: C, 67.8; H, 5.3. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

2-Hydroxymethyl-3-(2-hydroxy-4,6-dimethoxyphenyl)-6-methoxycoumarone was similarly prepared from 6′, 5, 7-trimethoxycoumarono-(2′, 3′-3, 4)- coumarin (m.p. 255°) and obtain-

ed from benzene in fine prisms, m.p. 168°; yield 50%. (Found: C, 65.6; H, 5.7. $C_{18}H_{18}O_6$ requires C, 65.4.; H, 5.5%).

7′-Methoxychromeno-(3′,4′-2,3)-coumarone.—A solution of 2-hydroxymethyl-3-(2-hydroxy-4-methoxyphenyl)-coumarone (1.0 g.) in pure diethylene glycol (30 c.c.) was heated under reflux for 25 minutes. During boiling slow separation of water was noted. The mixture was cooled, diluted with water, extracted with ether, and washed with alkali. After drying ($MgSO_4$), ether was removed to yield the *chromene* (0.6 g.), which crystallised from ethanol in voluminous fluffy needles, m.p. 69-71°. (Found: C, 76.1; H, 5.0. $C_{16}H_{12}O_3$ requires C, 76.2; H, 4.8%). λ_{max}, 231 mμ (log ε 4.41), 265mμ (log ε 4.03), and 301 mμ (log ε 3.84).

The compound exhibits a deep red coloration with sulphuric acid. On treating the solution of the compound in acetic acid with bromine vapour, the solution becomes transient red with the separation of a yellow solid (pyrylium bromide). A solution of the compound in boiling acetic acid on treatment with one molecular proportion of triphenylmethyl perchlorate gave *7′-methoxycoumarono-(2,3-3′,4′)-benzopyrylium perchlorate* as brownish yellow crystals, m.p. 220° (explosion). On crystallisation from acetic acid the compound deteriorates and a brownish product is obtained, m.p. 215° (explosion).

5′,7′-Dimethoxychromeno-(3′,4′-2,3)-coumarone was similarly prepared and obtained from ethanol in colorless crystals, m.p. 105-106°, showing a red coloration with sulphuric acid. (Found: C, 72.0; H, 5.2. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%). λ_{max} 220 mμ (log ε 4.46) and 272 mμ (log ε 4.03). The corresponding *pyrylium prchlorate* was obtained as orange-red needles, m.p. 232° (decomp.). (Found: C, 54.1; H, 3.7. $C_{17}H_{13}O_8Cl$ requires C, 53.6; H, 3.4%).

6,7′-Dimethoxychromeno-(3′,4′-2,3)-coumarone.—A solution of 2-hydroxymethyl-3-(2-hydroxy-4-methoxyphenyl)-6-methoxycoumarone (0.2 g.) in diethylene glycol (5 c.c.) was boiled for only 2 minutes. The product was worked up as before to give the *chromene* (0.1 g.), which crystallised from ethanol in small prisms, m.p. 140°. (Found: C, 72.2; H, 4.9. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%). λ_{max} 242 mμ (log ε 4.44), 248 mμ (log ε 4.44), 271mμ (log ε 3.84), and 290 mμ (log ε 3.98).

The compound develops with sulphuric acid a light pink colour, exhibiting a strong green fluorescence and with strong nitric acid it shows a crimson colour. With bromine vapour a solution of the compound in acetic acid forms an attractive crimson solution with the separation of an unstable crimson, crystalline solid. The red colour very slowly fades away and changes to light yellow. This change takes place quickly on adding a few drops of acetone.

On boiling a solution of the compound in acetic acid with crystalline ferric chloride, the solution turns red with the separation of a fine crystalline precipitate of *6′,7-dimethoxycoumarono-(2′,3′-3,4)-benzopyrylium ferrichloride*. This was collected, washed with a small quantity of acetic acid, and obtained as a light orange crystalline mass, m.p. 215° (decomp.). (Found: C, 42.1; H, 3.0. $C_{17}H_{13}O_4FeCl_4$ requires C, 42.6; H, 2.7%).

The corresponding *perchlorate* was prepared by boiling a solution of the chromene (0.05 g.) in dry acetic acid (2 c.c.) with triphenylmethyl perchlorate (0.05 g.) for 1 minute. The resulting deep green fluorescent solution on cooling deposited the brownish pyrylium salt, which was collected and washed with acetic acid, m.p. 239° (explosion).

6,5,7′-Trimethoxychromeno-(3′,4′-2,3)-coumarone—This *chromene* was prepared as above, the period of heating being reduced to 1 minute. The compound crystallised from ethanol in light colorless needles, m.p. 127°; yield, 85%. (Found: C, 68.9; H, 5.1. $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.2%). λ_{max} 242 mμ (log ε 4.40) and 288 mμ (log ε 3.96). The compound develops a dark pink colour with sulphuric acid and a crimson solution with bromine vapour in acetic acid. The corresponding *pyrylium perchlorate* was obtained as before in greyish brown plates, m.p. 231° (decomp.). (Found: C, 53.2; H, 4.1. $C_{18}H_{15}O_9Cl$ requires C, 52.6; H, 3.7%).

cis-*7′-Methoxychromano-(3′,4′-2,3)-coumaran*.—A solution of 7′-methoxychromeno-(3′,4′-2,3)-coumarone (0.2 g.) was hydrogenated in acetic acid in presence of palladised charcoal (0.2 g., 5%) at the room temperature and atmospheric pressure. The absorption of hydrogen was complete in 3 hours. The *chroman* (0.15 g.) crystallised from ethanol in prisms, m.p. 95-96°. (Found: C, 75.2; H, 5.5. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.5.%). λ_{max}, 282 mμ (log ε 3.58). The compound develops a dark brown colour with sulphuric acid. The chroman also gave the related pyrylium salt, m.p. 220°, mentioned before, on treatment with triphenylmethyl perchlorate. On heating the compound with palladised charcoal, a small quantity of a material was obtained which gave a red coloration with sulphuric acid, indicating that the compound might be readily dehydrogenated.

cis-*6,7′-Dimethoxychromano-(3′,4′-2,3)-coumaran* was similarly prepared from the corresponding chromene by hydrogenation and obtained as colorless needles, m.p. 125° from ethanol. (Found: C, 71.6; H, 5.7. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.7%). λ_{max} 287 mμ (log ε 3.84).

cis-*6,5′,7′-Trimethoxychromano-(3′,4′-2,3)-coumaran* was prepared by the catalytic hydrogenation of the related chromene and obtained from ethanol in colorless prisms, m.p. 104°. (Found: C, 68.6; H, 6.0. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.8%). λ_{max} 286 mμ (log ε 3.63).

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Monoterpenoids. Part III.* Ring Enlargement of Tetrahydrocarvone†

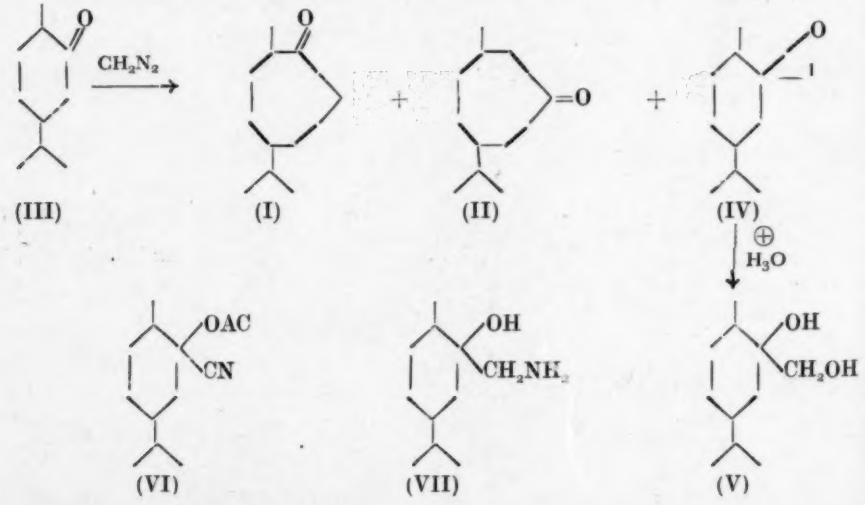
T. M. Jacob and Sukh Dev**

Ring-expansion of tetrahydrocarvone has been studied by the diazomethane method and by the Tiffeneau-Demjanov semipinacolic deamination. The first method yielded a mixture of ketones (30%) consisting of 2-methyl-5-isopropylsuberone (~44%) and 3-methyl-6-isopropylsuberone (~56%); formation of the spiro- ∝ -epoxide to the extent of 28% took place. The semipinacolic deamination method also, as anticipated, yielded an identical mixture of the suberones.

2-Methyl-5-isopropylsuberone (I) and 3-methyl-6-isopropylsuberone (II) are important intermediates in certain azulene synthesis (Jacob and Sukh Dev, *Chem. & Ind.*, 1956, 576; Dutta, this *Journal*, 1957, **24**, 761) and their systematic syntheses have been described (Jacob and Sukh Dev, this *Journal*, 1957, **24**, 327; cf. Dutta, *ibid.*, 1956, **33**, 885). The present investigation was undertaken to ascertain the ratio of (I) and (II) resulting in a ring-expansion reaction of tetrahydrocarvone (III).

Ring Enlargement by Diazomethane

This method of ring-expansion has recently been reviewed (Gutsche, "Organic Reactions", 1954, **8**, 364). The reaction was carried out by the nitrosomethylurethane method, according to the general directions of Meerwein (German Patent 579,309).



* Part II: This *Journal*, 1957, **34**, 327.
† Abstracted from the Ph.D thesis (Madras, 1956) of T. M. Jacob.
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The yield of the ring-expanded material was about 30% and about 28% of the starting ketone was recovered; formation of the oxide (IV) to the extent of 28% was demonstrated by hydrolysis to the glycol (V). The composition of the suberone fraction was established as 44%(I) and 56%(II) by quantitative infrared spectrophotometry (*vide infra*).

Ring Enlargement by the Tiffeneau Rearrangement

The Tiffeneau rearrangement (Tiffeneau, Weil, and Tchoubar, *Compt. rend.*, 1937 **205**, 54; Tchoubar, *ibid.*, 1941, **212**, 195; *Bull. Soc. Chim.*, 1949, 160, 164, 169), which is a special case of the Demjanov reaction, has sometimes been used with advantage for the ring-expansion of cyclic ketones (Ruzicka, Plattner, and Wild, *Helv. Chim. Acta*, 1943, **26**, 1631; Gutsche, *J. Amer. Chem.*, 1949, **71**, 3513; Cope, Nace, and Estes, *ibid.*, 1950, **72**, 1123; Dauben *et al.*, *ibid*, 1951, **73**, 2359; Roberts and Gorham, *ibid.*, 1952, **74**, 2278; Blicke and co-workers, *ibid.*, 1953, **75**, 2924, 5418; Wendler, Taub, and Slates, *ibid.*, 1955, **77**, 3559). Tetrahydrocarvone (III) was converted into the cyanohydrin and thence to the acetate (VI) in an overall yield of 99%. The reduction of the cyanohydrins with lithium aluminium hydride has been reported (Nace and Smith, *J. Amer. Chem. Soc.* 1952, **74**, 1861), but we have preferred to use the acetate for reduction in order to reduce chances for the formation of any tetrahydrocarvol through a retrogression (under alkaline conditions of the reaction) of the cyanohydrin and subsequent reduction of the resulting ketone (cf. H. C. Neumann, E. T. H. Dissertation, Zürich, 1949). The same situation can, however, arise if the reduction of the acetate function occurred first (Roberts and Gorham, *loc. cit.*). The yield of the ring-expanded material was 70%; the glycol (V) could also be isolated to the extent of 12%.

In a previous publication (Jacob and Sukh Dev, *loc. cit.*) it has been pointed out that the ketone (I) has two characteristic bands at 915 and 893 cm^{-1} and these could be utilised for their estimation* in a mixture. The infrared spectra of the ketone-mixture, obtained by the two methods, were almost superimposable. The percentage of the ketone (I) in the mixture was estimated from its absorption at 893 cm^{-1} and that of ketone (II) from its absorption at 865 cm^{-1}, by following the usual procedure (e.g. vide Tunniclift *et al.*, *Anal. Chem.*, 1949, **21**, 890). The results show that the suberone mixtures, obtained in both the processes, contain 44% (I) and 56% (II).

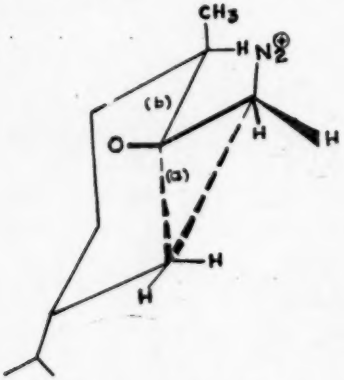
The migration of the groups in a molecular rearrangement is governed by stereo-electronic factors. In the case under study, the formation of (I) or (II) will depend on which of the bonds (*i.e.*, the residual groups with its bonding electrons) (*a*) or (*b*) moves. It would appear that in the present instance, electronic factors being almost identical†, the movement will be essentially determined by steric factors.

The intermediate, resulting from the nucleophilic attack of diazomethane on the carbonyl group, can be represented as a diazonium betain (Arndt and Eistert, *Ber.*, 1935, **68**,

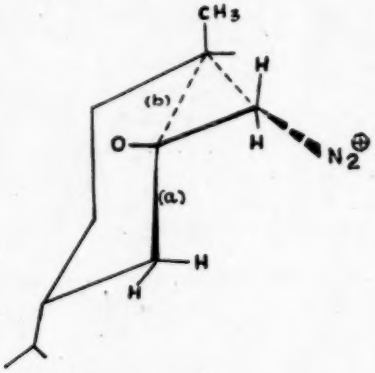
* In an attempt to use the method of vapour-phase chromatography for this analysis, it was found that both the ketones had the same retention times under a variety of experimental conditions (temperature, columns, gas, etc.).

† The present results could possibly be explained by a slight preference of the bond (*b*) to migration due to the induction effect of the methyl group. That this is not so, is clear from several examples in the literature (e.g. vide Wendler, Taub, and Slates, *J Amer. Chem. Soc.*, 1955, **77**, 3559; Birch and Harrison, *Austrl. J. Chem.*, 1955, **8**, 519) in which the methylene group has preferentially migrated.

196). Since, a similar intermediate has been postulated in the reaction of nitrous acid with a β-amino alcohol (Mckenzie and Richardson, *J.Chem. Soc.*, 1923, **123**, 79) it was anticipated, as actually realised, that the Tiffeneau rearrangement would yield a mixture of ketones, essentially identical with that obtained in the dizomethane reaction. The decomposition of the intermediate can occur either by a synchronous electron-transfer process or by a stepwise sequence involving a carbonium ion. Sufficient evidence has been gathered (McCasland, *J. Amer. Chem. Soc.*, 1951, **73**, 2293; Curtin and Crew, *ibid.*, 1955, **77**, 354; Curtin and Schmukler, *ibid.*, 1955, **77**, 1155; Ramirez and Stafiej, *ibid.*, 1956, **78**, 644; Curtin, *Record Chem. Prog.*, 1954, **15**, 111) to show that in the nitrous acid deamination of β-amino alcohols, the nitrogen-release occurs through a concerted one-step process, involving a back-side attack on the carbon bearing the diazonium groups. Probably the same path is followed by the diazomethane ring-enlargement reaction (Robinson and Smith, *J. Chem. Soc.*, 1937, 371). Two configurations (VIII) and (IX) are possible for the transition state in the ring-expansion of carvomenthone*, which meet the requirements of the principle of the co planarity of the centres involved in a synchronous reaction (Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066; Barton and Rosenfelder, *J. Chem. Soc.*, 1951, 1048).



(VIII)



(IX)

Configuration (VIII) will lead to the suberone (I) and (IX) would result in (II). In the configuration (VIII), the relatively bulky diazonium group is placed skew to the oxygen and the -$CHCH_3$ on the next carbon, whereas in (IX), it is skew to the oxygen and the -CH_2- and a hydrogen atom becomes skew to the oxygen and the -$CHCH_3$ group; thus the conformation in (IX) would be energetically favoured, at least, to some extent. The energy-difierences of (VIII) and (IX) cannot, however, be large and in the ring-expansion reaction, a small excess of (II), as actually realised, is to be expected.

EXPERIMENTAL

All melting and boiling points are uncorrected. Anhydrous sodium sulphate was used for drying the extracts. The infrared measurements were carried out on a Perkin-Elmer double-beam instrument with sodium chloride optics.

*The tetrahydrocarvone used in these experiments has been estimated to be at least 75% (-) -carvomenthone (Read and Johnston, *J. Chem. Soc.* 1934, 226). The bulkier diazonium methyl group has been shown in the equatorial conformation; the treatment discussed can apply equally well, and with similar results, to the other epimer.

Action of Diazomethane on Tetrahydrocarvone.—A mixture of tetrahydrocarvone (77.4 g., 0.5 *M*) (Jacob and Sukh Dev, this *Journal*, 1957, **34**, 332), anhydrous aldehyde-free methanol (200 c.c.), and anhydrous potassium carbonate (2 g.) was placed in a 3-necked flask (1 litre) fitted with a stirrer, thermometer, dropping funnel, and an exit tube. Nitrosomethylurethane (56 c.c., 63.3 g., 0.48*M*) was added to the above stirred mixture during 5 to 6 hours, the temperature of the reaction having been maintained at 20-25° by suitably cooling the flask, when required. After leaving overnight (16 hours) as such, the product was filtered from potassium carbonate and the low-boiling material distilled (water-bath/50 mm). The residue was fractionated through an efficient column to give: (*i*) b.p. 84-88°/5 mm, mostly at 84°, n_D^{25} 1.4350-1.4570, yield 45 g.; (*ii*) b.p. 88-95°/5 mm, n_D^{25} 1.4580, yield 4.2 g.; (*iii*) b.p. 95-98°/5 mm, chiefly at 98°, n_D^{25} 1.4610—1.4620, yield 25 g.; (*iv*) a residue.

The third fraction represented the ring-expanded material. It was redistilled to give a product: b.p. 98°/5 mm, n_D^{25} 1.4616, $[\alpha]_D^{25}$ -12°.6. (Found: C, 78.17; H, 11.78. $C_{11}H_{20}O$ requires C, 78.57; H, 11.91%).

The first fraction was a mixture of tetrahydrocarvone and the oxide (IV). This was established as follows: This material (3.85 g) was stirred at room temperature (20-25°) with 4% H_2SO_4 (50 c.c.) for 64 hours, then saturated with ammonium sulphate and extracted with ether (15 c.c. × 5). After drying, the solvent was removed and the residue fractionated to give a fore-run (b.p. 68-75°/2 mm, n_D^{25} 1.4550, yield 1.15 g.), identified as tetrahydrocarvone, and a high-boiling product, b.p. 158-65°/ 2 mm, n_D^{25} 1.4780, yield 2.0 g. The latter was fractionated and the cut with b.p. 160°/2 mm., n_D^{25} 1.4800 analysed. It gave a positive test with periodic acid (Shriner and Fuson, "The Systematic Identification of Organic Compounds", John Wiley, New York, 1948, p. 115). (Found: C, 70.75; H, 11.8. $C_{11}H_{22}O_2$ requires C, 70.98; H, 11.82%).

In this experiment when excess of nitrosomethylurethane (1.6 *M* for 1 *M* of tetrahydrocarvone) was used, the yield of the ring-expanded material was 45% (based on the ketone).

1-*Cyano*-2-*methyl*-5-*isopropylcyclohexyl Acetate* (VI).—To well-cooled (ice-salt) tetrahydrocarvone (15.3 g., 0.1*M*) liquid hydrogen cyanide (7.5 c.c., 0.18 *M*) was added all at once. To this powdered potassium cyanide (0.1g.) and diethylamine (2 drops) were added. The reaction mixture was kept at 0 to 5° for 24 hours, chilled to -5°, and the base neutralised with phosphoric acid (*d* 1.75, 1 c.c.). The product was diluted with anhydrous ether (20 c.c.) and a chilled mixture of acetic anhydride (25 c.c.) and acetyl chloride (1.5 c.c.) added. This was left aside at 0° for 48 hours and then at room temperature (20-25°) for one week. The excess of acetic anhydride, etc. was removed (column) and the residue was carefully fractionated to obtain the required compound as a colorless liquid, b.p. 120°/2mm, $n_D^{24.5}$ 1.4535—1.4605, yield 22.1g.(99.7%).

An analytical sample had: n_D^{24} 1.4595,d_4^{25} 0.9895, M_D 61.66 (calc. 61.44). (Found: N, 6.7. $C_{13}H_{21}O_2N$ requires N, 6.3%.)

1-*Hydroxy*-2-*methyl*-5-*isopropylcyclohexylmethylamine* (VII).—Lithium aluminium hydride (7.2 g., 0.19 *M*) was placed in a one-litre 3-necked flask, and at once covered with anhydrous ether (250 c.c.). This was stirred under anhydrous conditions to get a fine slurry (1/2 hour). A solution of the cyanohydrin acetate (19.2 g., 0.086 *M*) in ether (80 c.c.) was let in with stirring at a rate that the refluxing could be controlled (20 minutes). After gently refluxing for 1½ hours, the reaction mixture was left overnight (16 hours). The reaction

mixture was well-chilled in ice-salt and the excess of lithium aluminium hydride destroyed by the addition of ice-water (20 c.c.). To this a solution of sodium potassium tartrate (20%, 500 c.c.) was added to decompose the complex. After stirring for 1 hour at room temperature, the turbid solution was extracted with ether (100 c.c. × 5) and the extract dried. The solvent was flashed off, the last traces under suction on a water bath. The crude amine (16. g., 100.4%), thus obtained, was directly used for the next step.

Deamination with Nitrous Acid.—The above crude amine (16 g.) was dissolved in water (110 c.c.) containing acetic acid (8 c.c.); a slight insoluble material was removed. To this solution, well cooled in ice, a solution of sodium nitrite (8 g., 0.12 *M*) in water (50 c.c.) was added during 20 minutes with stirring. The stirring was continued for another 2½ hours at 0° and then for ½ hour at room temperature (25°), and finally on a steam-bath for 45 minutes. The cooled reaction mixture was extracted with ether (50 c.c. × 5), washed with brine, and dried. After removal of the solvent the residue was fractionated: ((*i*) b.p. 110-19°/40 mm, n_D^{28} 1.4575 yield 0.7 g.; (*ii*) b.p. 119-24°/40 mm, n_D^{28} 1.4595, yield 4.2 g.; (*iii*) b.p. 125-28°/40 mm, n_D^{28} 1.4615, yield 5.9 g.; (*iv*) 120-60°/2 mm, n_D^{28} 1.4850, yield 1.92 g.

The first fraction was rejected. Fractions (*ii*) and (*iii*) represented the ring-expanded material. These cuts were mixed up and precisely refractionated to remove some alcohol impurity (infrared absorption at 3521 cm^{-1}; possibly tetrahydrocarvol), when it had b.p. 97-98°/5 mm. (Found: C, 78.53; H, 11.92. $C_{11}H_{20}O$ requires C, 78.57; H, 11.91%).

The fourth fraction was redistilled to give a viscous liquid, b.p. 150-55°/1 mm, n_D^{28} 1.4850; it gave a positive test with periodic acid. (Found: C, 71.06.; H, 11.83. $C_{11}H_{22}O_2$ requires C, 70.98; H, 11.82%).

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Studies on Colour and Constitution: Applications of Forster's Rule

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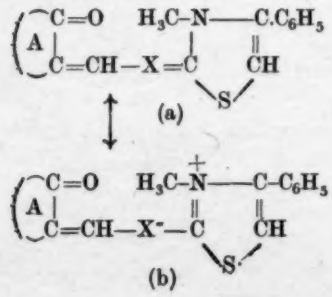
Relative acidities and basicities of a series of heterocyclic nuclei have been evaluated with the help of absorption maxima data of the following groups of compounds:

(*i*) Dimethin merocyanines and their aza analogues.
(*ii*) *p*-Dialkylaminobenzylidene derivatives of ketomethylene compounds and their aza analogues.
(*iii*) *p*-Dialkylaminostyryl dyes and their aza analogues.
(*iv*) Unsymmetrical cyanines and their aza analogues.

Brooker (*Rev. Mod. Phys.*, 1942, **14**, 275) devised a method based on "deviation" for estimating the relative basicities and acidities of the various heterocyclic nuclei. In the present work, the relative basicities and acidities of a series of heterocyclic basic or acidic nuclei have, been determined however, with the help of Forster's rule (Z. *Elektrochem.*, 1939, **45**, 548). The method is based on absorption shift for replacement of =CH— by =N— in the chromophoric chain linking the heterocyclic nuclei concerned. Forster's rule states that the absorption maximum of a dye will increase with the decreasing tendency of the chain of atoms (chromophores) to take up the characteristic charge. The chromophoric atoms carry charges only in the excited state and the nature of the charge and their relative contributions largely depend on their energies.

Estimation of Relative Acidities

Determination of the relative acidities of a series of heterocyclic ketomethylene nuclei by this method has been accomplished by studying the absorption shift involved in the structural change from =CH— to =N— in dimethin merocyanines (I: X =CH, N). The desired dimethin merocyanine (I: X =CH) was prepared by two methods, viz., (*i*) by condensing 5-ethoxymethylene-ketomethylene compound (formed by reaction of ethyl orthoformate and the keto methylene compound) with 4-phenyl-2-methylthiazole methiodide and (*ii*) by condensing the ketomethylene compound with 2-(2-acetanilidovinyl)-4-phenylthiazole methiodide (Rout and Patnaik, this *Journal*, 1957, **34**, 543). The corresponding aza analogue (I: X =N) was prepared by condensing the ethoxymethylene derivative with 4-phenyl-2-aminothiazole methiodide.



(I)

In (I) the excited structure carrying X^- has greater significance than structures carrying X^+ because of the presence of one more double bond in the former than in the latter one. Therefore, for the replacement of X=CH by X=N, the relative contribution of (Ib:X=N) to the resonance hybrid will be more than (Ib:X=CH) because of greater stability of $-N^-$ in comparison to $—CH_2^-$. Therefore, in accordance with Forster's rule, a hypsochromic shift is predicted for such structural change in (I).

As, in the above compounds, the hypsochromic shift is due to the increased significance of the excited structure, it follows that with increase in acidity (*i.e.*, electron attracting property) of the nucleus A, the contribution of the excited structure (Ib) to the resonance hybrid would be diminished. In other words, in a series of dyes derived from weakly acidic nuclei and a fixed basic nucleus, as the acidity of the acidic nucleus is gradually increased, the amount of hypsochromic shift will gradually decrease. From examination of the data in Table I, it would appear therefore that the acidic nuclei may be arranged in order of decreasing acidity as follows: isoxazolone >pyrazolone >rhodanine.

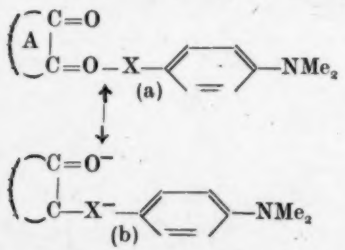
TABLE I

Shift for replacement of =CH— *by* =N— *in dimethin merocyanine.*

Nature of nucleus A in(I).	Absorption maxima (mμ).		Observed shift.
	X=CH.	X=N.	
3-Phenylrhodanine	510	485	-25 mμ
1-Phenyl-3-methylpyrazolone	501	490	-11
3-Phenylisoxazolone	496	490	-6

N.B. Expected shift: Hypsochromic.

The relative acidities have also been evaluated from the shift in absorption maxima for replacement of =CH– by =N— in the *p*-dialkylaminobenzylidene derivatives of ketomethylene compounds (II: X=CH). The *p*-dialkylaminobenzylidene derivatives were obtained by condensing the ketomethylene compounds with *p*-dialkylaminobenzaldehyde. Their aza analogues (II: X=N) were obtained by using *p*-nitrosodialkylaniline in place of *p*-dialkylaminobenzaldehyde for condensation with ketomethylene compounds.



(II)

In such a case, by applying considerations as applied to the β-anilinovinyl derivatives and its aza analogue (Knott and Williams, *J. Chem. Soc.*, 1951, 1586), the most likely excited structure involves $-X^+-$ and not $-X^-$- as in (I). Consequently, for replacement of =CH— by =N–, the characteristic charge would change from $-CH^+-$ to $-N^+-$ and because of the greater stability of $-CH^+-$ in comparison to $-N^+-$, the contribution of the interauxochromic, ionic excited structure to the resonance hybrid would increase or, in other words, Forster's rule predicts a bathochromic shift for replacement of =CH—by =N—in (II). This is actually

observed. The bathochromic shift in these dyes is mainly caused due to the decreased significance of the excited structure (IIb). The significance of the latter would increase with increase in acidity of the nucleus A. In other words, the bathochromic shift will gradually increase. The acidic nuclei constituting the dye in Table II may be arranged in the decreasing order of acidity as: isoxazolone > pyrazolone > rhodanine > thiohydantoin.

TABLE II

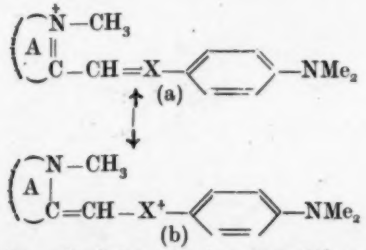
Shift for replacement of =CH—*by*=N— *in* p-*dialkylaminobenzylidene derivatives of ketomethylene compound.*

Nature of nucleus A in (II).	Absorption maxima. X=CH.	X=N.	Observed shift.
3-Pehnylisoxazolone	490 mμ	545 mμ	+55 mμ
1-Phenyl-3-methylpyrazolone	470	520	+50
3-Phenylrhodanine	480	505	+25
3-*m*-Tolyl-3-thiohydantoin	450	470	+20

N.B. Expected shift: Bathochromic.

Estimation of Relative Basicities

The relative basicities (electron donating ability) of a series of heterocyclic nuclei can be assessed from the shift resulting from the structural change from =CH—to =N—in the *p*-dialkylaminostyryl dyes (III: X=CH) derived from such nuclei. The styryl dye (III: X=CH) was prepared by condensing the quaternary salt with *p*-dialkylaminobenzaldehyde. The corresponding aza analogue (III: X=N) was obtained by using *p*-nitrosodialkylaniline.



(III)

Here also, the most likely excited structure involves -X^+- as in (II). Hence by applying the considerations made above, a bathochromic shift will be observed for such compounds (III) for a structural change from =CH—to =N—. The bathochromic shift will be gradually increased as the basicity of the nucleus, forming the dye, is decreased. From the results in Table III, the basic nuclei may therefore be arranged in order of decreasing basicity as: pyridine-2 > 4-*p*-bromophenylthiazole, 4-*p*-chlorophenylthiazole > 4-phenylthiazole > quinoline-2.

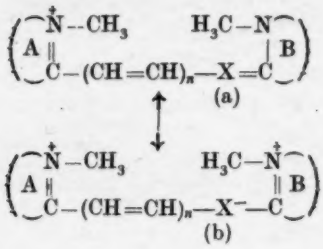
TABLE III

Shift for replacement of =CH— *by* =N— *in* p-*dimethylaminostyryl dyes.*

Nature of nucleus A (in III).	Absorption maxima. X=CH.	X=N.	Observed shift.
Quinoline-2	527 mμ	590 mμ	+63 mμ
4-Phenylthiazole	490	540	+50
4-*p*-Bromophenylthiazole	490	530	+40
4-*p*-Chlorophenylthiazole	490	530	+40
Pyridine-2	459	490	+31

N.B. Expected shift: Bathochromic.

The relative basicities of a series of basic nuclei have also been assessed with the help of shift in absorption maximum for such structural change from =CH— to=N— in unsymmetrical cyanines (IV: X=CH).



(IV)

The unsymmetrical cyanines were prepared according to the method of Brooker *et al.* (*J. Amer. Chem. Soc.*, 1942, **64**, 199) and the corresponding aza analogues by the method of Knott and Williams (*loc. cit.*). By applying considerations as in (J), the replacement of =CH—by =N—would result in a hypsochromic shift, which is due to the relatively large contribution to the resonance hybrid of the excited structure (IVb: X=N) as compared to that of (IVb: X=CH).

In the contribution of the latter structure (IVb), charge separation is required, which will naturally be facilitated with increasing basicity of nucleus B. There will be therefore increase in hypsochromic shift with increasing basicity of the nucleus. This effect in the cyanine series is illustrated in Table IV.

TABLE IV

Shift for replacement of =CH— *by* =N— *unsymmetrical cyanines.*

Nature of nucleus. A in (IV).	B in (IV).	Value of *n*.	Absorption maxima. X=CH.	X=N.	Observed shift.
Benzothiazole	4-Phenylthiazole	0	418 mμ	375 mμ	-43 mμ
Quinoline-2	,,	0	475	405	-70
Benzothiazole	,,	1	540	470	-70
Quinoline-2	,,	1	600	520	-80
Benzothiazole	4-*p*-Bromophenylthiazole	2	640	570	-70
,,	4-Phenylthiazole	2	640	565	-75
,,	4-*p*-Bromophenylthiazole	2	640	560	-80
,,	4-*p*-Ethoxyphenylthiazole	2	640	560	-80
Quinoline -2	4-Phenylthiazole	2	700	590	-100
,,	4-*p*-Bromophenylthiazole	2	..	590	-110
Benzothazole	4-Phenylthiazole	3	740	655	-85
,,	4-*p*-Ethoxyphenylthiazole	3	740	650	-90
Quinoline-2	4-Phenylthiazole	3	790	670	-120
,,	4-*p*-Bromophenylthiazole	3	790	670	-120

N.B. Expected shift: Hypsochromic.

EXPERIMENTAL

5-(3'-Methyl-4'-phenylthiazolin-2'-ylidene-aminomethylene) – 3-phenylrhodanine.— A mixture of 4-phenyl-2-aminothiazole methiodide (1.6 g.) and of 5-ethoxymethylene-3-phenylrhodanine (1.35 g.) was boiled in absolute ethanol and triethylamine for 25 minutes. The product separated on cooling after removal of excess of the solvent. Recrystallisation from methanol gave lustrous golden needles, m.p. 300°, yield 54%. (Found: C, 58.37; H, 3.72. $C_{20}H_{15}ON_3S_3$ requires C, 58.53; H, 3.90%). The analytical data of the other aza analogues of merocarbocyanines are recorded in Table VA.

5-(p-Dimethylamino-anilinomethylene)-3-phenylrhodanine.—A mixture of 3-phenylrhodanine (1.05 g. and *p*-nitrosodimethylaniline (0.75 g.) was boiled in absolute ethanol in presence of piperidine (2 drops) for 40 minutes. Removal of the solvent at atmospheric pressure resulted in the separation of 1.3 g. of the product. Recrystallisation from ethanol gave red plates, m.p. 145°, yield 65%. (Found: C, 59.72; H, 4.33. $C_{17}H_{15}ON_3S_3$ requires C, 59.81; H, 4.41%). The analytical data of the other such compounds are shown in Table VB.

2-(p-Dimethylamino-anilinomethylene)-3-methyl-4-p-bromophenylthiazole Methiodide.– A mixture of 4-*p*-bromophenyl-2-methylthiazole methiodide (2.0 g.) and *p*-nitrisodimethylaniline (0.75 g.) was boiled in absolute ethanol in presence of piperidine (2 drops) for 30 minutes. The desired product (2 g.) separated out on cooling. Recrystallisation from ethanol furnished lustrous violet crystals, m.p. 193°, yield 55%. (Found: C, 43.18; H, 3.56. $C_{19}H_{19}N_3BrIS$ requires C, 43.00; H, 3.40%). The analytical data of the other such dyes are recorded in Table VC.

TABLE V

Nature of nucleus A in (I).	M. P.	Yield.	Formula.	% Carbon. Found.	% Carbon. Calc.	%Hydrogen. Found.	%Hydrogen. Calc.
A. Aza analogues of dimethin merocyanines.							
3-Penylisoxazolone	182-84°	52%	$C_{20}H_{15}O_2N_3S$	60.78	61.06	3.60	3.81
1-Phenyl-3-methyl-pyrazolone	176-77°	56	$C_{21}H_{18}ON_4S$	67.12	67.37	4.64	4.81
B. Aza analogues of *p*-dimethylaminobenzylidene derivatives of ketomethylene compounds.							
3-Phenylisoxazolone	138°	70	$C_{17}H_{15}N_3O_2$	69.50	69.61	5.34	5.12
1-Phenyl-3-methyl-pyrazolone	147°	60	$C_{18}H_{18}ON_4$	70.43	70.60	5.64	5.88
3-*m*-Tolyl-2-thiohydantoin	249°	50	$C_{18}H_{18}ON_4S$	63.80	63.91	5.11	5.33
C. Aza analogues of *p*-demethylaminostyryl dyes.							
4-Phenylthiazole	209°	50	$C_{19}H_{20}N_3IS$	50.64	50.78	4.23	4.45
4-*p*-Chlorophenyl-thiazole	190°	55	$C_{19}H_{19}N_3SClI$	47.03	47.17	3.48	3.81
Quinoline-2	195°	50	$C_{19}H_{20}N_3I$	54.53	54.68	4.62	4.80
Pyridine-2	178°	50	$C_{15}H_{18}N_3I$	48.83	49.05	4.90	5.05

(5-*Methyl*-2-*benzothiazole*)[(3-*methyl*-2-(4-*phenylthiazole*)]-8 *azamethin Cyanine Iodide*.—A mixture of 4-phenyl-2-aminothiazole methiodide (3.2 g.) and 2-methylmercaptobenzothiazole methiodide (3.2 g.) was boiled in absolute ethanol in presence of triethylamine for 10 minutes. The desired product separated on cooling. Recrystallisation from methanol yielded straw-yellow crystals, m.p. 246°, yield 55%. (Found: C, 46.45; H, 3.44. $C_{18}H_8N_3IS_2$ requires C, 46.32; H, 3.29%).

(1-*Methyl*-2-*quinoline*)[(3-*methyl*-2-(4-*phenylthiazole*)]-10-*azatrimethin Cyanine Iodide*.—A mixture of 2-(2-acetanilidovinyl)-quinoline methiodide 1.32 g.) and 4-phenyl-2-aminothiazole methiodide (0.96 g.) was boiled in dry pyridine for 5 minutes. The desired product separated on addition of water. Two recrystallisations from ethanol gave red needles, m.p. 217-18°, yield 50%. (Found: C, 54.30; H, 4.01. $C_{22}H_{20}N_3IS$ requires C, 54.43; H, 4.12%).

(3-*Methyl*-2-*benzothiazole*) [3-*methyl*-2-(4-p-*methoxyphenylthiazole*)]–12-*azapentamethin Cyanine Iodide*.—A mixture of 2-(2-acetanilido-1, 3-butadienyl)-benzothiazole methiodide (2.3 g.) (Rout and Patnaik, this *Journal*, 1958, **35**, 511) and 4-*p*-methoxyphenyl-2-aminothiazole methiodide (1.75 g.) was boiled in dry pyridine for 6 minutes. The product separated on addition of ether. Recrystallisation from ethanol gave violet needles, m.p. 135°, yield 60%. (Found: C, 50.22; H, 3.91. $C_{23}H_{22}ON_3IS_2$ requires C, 50.46; H, 4.02%).

(3-*Methyl*-2-*benzothiazole*) [3-*methyl*-2-(4-p-*ethoxyphenylthiazole*)]–14-*azaheptamethin Cyanine Iodide*.—A mixture of 4-*p*-ethoxyphenyl-2-aminothiazole methiodide (1.08 g.) and 2-(acetanilido-1,3,5-hexatrienyl)-benzothiazole methiodide (1.47 g.) (Rout and Patnaik, *loc. cit.*) was boiled in absolute ethanol and triethylamine for 2 minutes. The desired product separated on chilling. Recrystallisation from ethanol gave green crystals, m. p. 212-13°, yield 45%. (Found: C, 53.02; H, 4.22. $C_{26}H_{26}ON_3IS_2$ requires C, 53.16; H, 4.43 %). The analytical data of other unsymmetrical azacyanines are shown in Table VI.

TABLE VI

Unsymmetrical azacyanines.

Nature of nucleus A in (IV).	Nature of nucleus B in (IV).	Value of *n*	M.P.	Yield.	Formula.	%Carbon.		%Hydrogen.	
						Found.	Calc.	Found.	Calc
Quinoline-2	4-Phenylthiazole	0	247-48°	50%	$C_{20}H_{18}N_3IS$	52.20	52.79	3.81	3.93
Benzothiazole	,,	1	210-11°	50	$C_{20}H_{18}N_3IS_2$	48.64	48.87	3.50	3.66
,,	Benzothiazole	2	250-61°	40	$C_{22}H_{22}N_3IS_2$	50.70	50.86	4.10	4.24
,,	4-Phenylthiazole	2	160°	50	$C_{22}H_{20}N_3IS_2$	50.90	51.06	3.64	3.87
,,	4-*p*-Bromophenylthiazole	2	185-86°	60	$C_{22}H_{19}N_3BrIS_2$	44.16	44.30	3.03	3.19
,,	4-*p*-Ethoxphenylthiazole	2	175-76°	50	$C_{24}H_{24}ON_3IS_2$	51.17	51.34	4.10	4.28
Quinoline-2	4-Phenylthiazole	2	195°	40	$C_{24}H_{22}N_3IS$	56.19	56.37	4.20	4.30
Benzothiazole	4-Phenylthiazole	3	175-76°	45	$C_{24}H_{22}N_3IS$	52.88	53.04	3.90	4.05
Quinoline-2	,,	3	210-12°	50	$C_{26}H_{24}N_3IS$	58.02	58.10	4.30	4.47

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Studies on the Solubilising Action of Quaternary Ammonium Group on Certain Organic Reagents and their Metal Complexes

N. K. Mathur and J. N. Gaur

The synthesis of certain organic reagents containing vic-dioxime, *N*-hydroxytriazene and hydroxyoxime groups have been described. The reagents under investigation contain a solubilising quaternary ammonium group [-$N(CH_3)_3Cl$] and yield with certain metal ions soluble complex cations rather than the usual precipitate. Two general methods have been used for introducing such groups in the molecules of oraganic reagents. In one of the methods, the original reagent containing tert-amino group is allowed to react with methyl iodide, but in the second method the reagent is subjected to chloromethylation followed by reaction with trimethylamine. This property has been utilised in preparing colour reagents suitable for spectrophotometric analysis. The properties of the reagents are compared with the parent precipitants and it has been shown that just like the sulphonic acid group, the quaternary amino group also does not change the chelating properetics of the organic reagents and the suitability of such group for solubilising metallo-organic complexes has been established.

Water solubility has been described as the most desirable characteristic of organic reagents used in inorganic analysis. In certain cases this characteristic has been achieved by the use of sulphonated derivatives of certain organic precipitant (Yoe, *J. Amer. Chem. Soc.*, 1932, **54,** 4139; Van Klooster, *ibid.*, 1921, **43,** 746). In general, such reagents are well suited for colorimetric analysis, because the introduction of such solubilising group yields water-soluble complex anion rather than the usual inner-complex precipitate with metal ions (Feigl, *Anal. Chem.*, 1949, **21,** 1289).

The acidic groups, such as -SO_3H, -COOH, and -OH (phenolic), appear to have been employed so far to solubilise the organic reagents and their metal complexes (Ephraim, *Ber.*, 1930, **63,** 1928). It was considered worthwhile to ascertain the capability of the quaternary ammonium group in solubilising metallo-organic complexes. Such groups are widely used in the molecules of synthetic detergents to render them water soluble. Solubilising action of such polar group is also observed in the Girard reagent (Girard and Sanclulesc, *Helv. Chim. Acta*, 1933, **19,** 1095) which is used to convert high-molecular weight steroid ketones into water-extractable hydrazone derivatives.

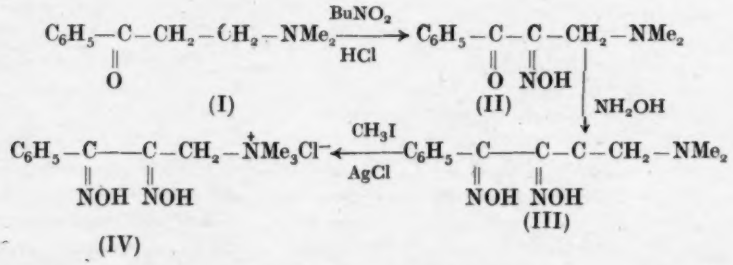
In the present paper a general survey of the methods used for the preparation of certain organic reagents, containing such solubilising groups has been done and the characteristics of such compounds as analytical reagents have been compared with the parent precipitants. Although -SO_3H group can be introduced into the molecules of organic reagents by a single process of sulphonation, the introduction of a quaternary ammonium group is not always easy. Two general methods have been used for the preparation of such compounds as are expected to have in their molecule groups, which are already known

to have chelate-forming properties with certain metal ions in addition to the solubilising groups.

In one of the methods, the starting compound already contained a tertiary amino group which was converted into the corresponding methiodide followed by reaction with freshly precipitated silver chloride, when the quaternary ammonium chloride was formed. The method is illustrated by the following examples involving the synthesis of a quaternary ammonium group containing vic-dioxime and a hydroxytriazene. As the primary object of the present investigation is to study the solubilising action of $-N(CH_3)_3Cl$ group, care has been taken to choose only those compounds of which the synthesis could be achieved easily by conventional and well-established methods.

EXPERIMENTAL

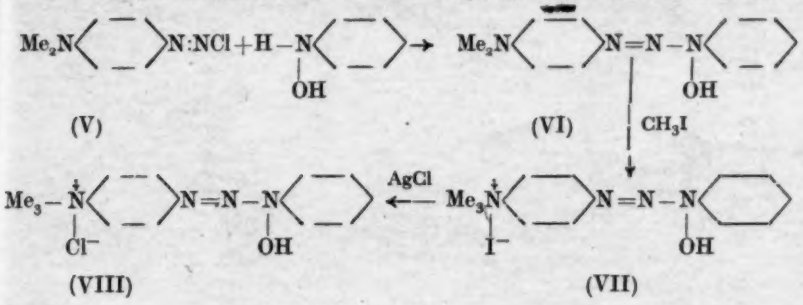
Synthesis of 3-Phenyl-2,3-dioximinopropyltrimethylammonium Chloride.—This compound was prepared from already-known tert-aminoketone, β-dimethylaminopropiophenone hydrochloride, obtained by the Mannich reaction. The aminoketone (I) containing a $-CO-CH_2-$group was converted into its isonitroso compound by reacting with calculated amount of butyl nitrite in ethanolic solution at 35-40°. The resulting diketone, monoxime (II), was converted into the dioxime (III) by refluxing with hydroxylamine sulphonate (1:1), previously neutralised with NaOH. On cooling the mixture, the dioxime separated, which was dried and allowed to stand with an excess of methyl iodide (1:3) for several hours, and the precipitated quaternary ammonium iodide (IV) was converted into the chloride by reacting with freshly precipitated silver chloride suspension in water. On evaporating the filtrate the final product (V) was obtained as a crystalline, water-soluble compound, decomposing at 166°. (Found: N, 15.46. Calc. for $C_{15}H_{22}O_2N_3Cl$: N,15.29%).



(I) (II) (III) (IV)

In ammoniacal medium the reagent gave a bright scarlet colour with Ni salts.

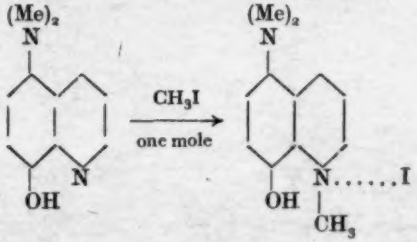
Synthesis of p-(3-*Hydroxy*-3-*phenyltriazeno*)-*phenyltrimethylammonium Chloride*.—This compound was synthesised by following Bamberger's method (*Ber.*, 1897, **30,** 2283), as modified by Sogani and Bhattacharya (*Anal. Chem.*, 1956, **29,** 1616). Diazotised *p*-aminodimethylaniline(V) was coupled with hydroxylamine at 5-10° with occasional addition of sodium acetate to prevent the solution from becoming too much acidic. The resulting 1-(*p*-dimethylaminophenyl)-3-hydroxy-3-phenyltriazene (VI) was converted into corresponding meth iodide (VII) by allowing it to stand for several hours with methyl iodide and finally the chloride salt (VIII) was obtained by reacting with freshly precipitated silver chloride.



The product decomposed at 184°. (Found: N, 17.82. Calc. for $C_{15}H_{19}ON_4Cl$:N, 18.27%).

In this qualitative reaction the product resembles 3-hydroxy-1-*p*-sulphonatophenyl-3-phenyltriazeine. The limitations of the above methods were observed in the following cases:

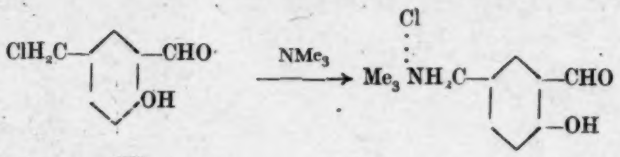
(1) The original compound contains an additional hetrocyclic tertiary nitrogen as in the case of 4-dimethylamino-8-quinolinol (IX) where the ring nitrogen preferentially undergoes quaternary ammonium salt formation and the resulting compound loses its chelating properties due to absence of a lone pair of electrons on the four-covalent N-atom



(IX)

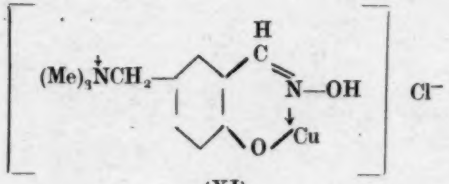
(2) In certain cases the teritary amino group could not be introduced easily into the molecules of already-known organic reagents and hence the quaternary ammonium compound could not be prepared. In such cases the known organic reagent is preferably subjected to chloromethylation provided that the compound contains an aromatic ring and the chloromethyl compound is converted into a quaternary ammonium compound by reacting with trimethylamine. The following example illustrates the application of the second method.

Synthesis of 3-Formyl-4-hydroxyphenylmethyltrimethylammonium Chloride.—Salicylaldehyde as well as its oxime has been used as reagents for certain metal ions (Welcher, "Organic Analytical Reagents", Vol. I, p. 397; Vol. III, p. 259, D. Van. Nostrand Co., New York). Chloromethylation of salicylaldehyde was reported by Stoermer and Behn (*Ber.*, 1901, **34**, 2455). When 4-Chloromethylsalicylaldehyde (X) was allowed to react with anhydrous trimethylamine in ether, corresponding quaternary ammonium salt was formed.



(X)

The oxime of the aldehyde (XI) is a quaternary ammonium group-substituted derivative of the well-known reagent salicylaldoxime and unlike the parent reagent it gives only a coloured complex with Cu^{2+}, which can be represented as



(XI)

Table I records comparative data of the three organic pricipitants and the corresponding colour reagents.

TABLE I

		Solubility in water.	Reaction with specific metal ions.	Optimum *p*H range.	Solubilising group.
Vic. Dioxime	Dimethylglyoxime	Insoluble	Scarlet ppt. of Ni complex	9-12	Nil
	3-Phenyl-2, 3-di-oximino-propyltrimethylammonium chloride	Soluble	Soluble pink Ni^{2+} complex	7.5-10	$-\overset{+}{N}(CH_3)_3Cl^-$.
N-Hydroxytriazene	1,3-Diphenyl-3-hydroxytriazene	Insoluble	Yellowish ppt. of Pd^{2+} complex	2-4	Nil
	3-Hydroxy-1-*p*-sulphonatophenyl-3-phenyltrizene	Soluble	Yellowish colour of soluble Pd^{2+} complex	2-4	$-SO_3H$.
	p-(3-Hydroxy-3-phenyltrizene)-phenyltrimethylammonium chloride	Do	Do	2-4	$-\overset{+}{N}(CH_3)_3Cl^-$.
Hydroxy-oxime	Salicylaldoxime	Insoluble	Greenish ppt. of Cu^{2+} complex	2.5-6	Nil
	2,3,4-Trihydroxyacetophenone oxime.	Soluble	Do	2-6	-OH(phenolic)
	Oxime of 3-formyl-4-hydroxyphenylmethyltrimethylammonium chloride	Do	Greenish colour of soluble Cu^{2+} complex	2-6.5	$-\overset{+}{N}(CH_3)_3Cl^-$.

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Guanylalkylureas and their Metallic Complexes. Part. VIII. Copper(II), Nickel(II), and Palladium (II) Complexes of Guanylalkoxyethylureas

R. L. Dutta and Subrata Lahiry

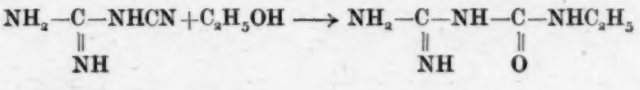
Dicyandiamide and alkoxyethanols (namely, methoxy-, ethoxy- and butoxyethanol) have been found to react in presence of copper acetate to form the rose-red coloured complex copper-bis-guanylalkoxyethylurea acetate. The reagents, guanylalkoxyethylurea sulphates, were obtained after decomposing the complex copper sulphates by H_2S. These respond to the usual tests of guanylureas.

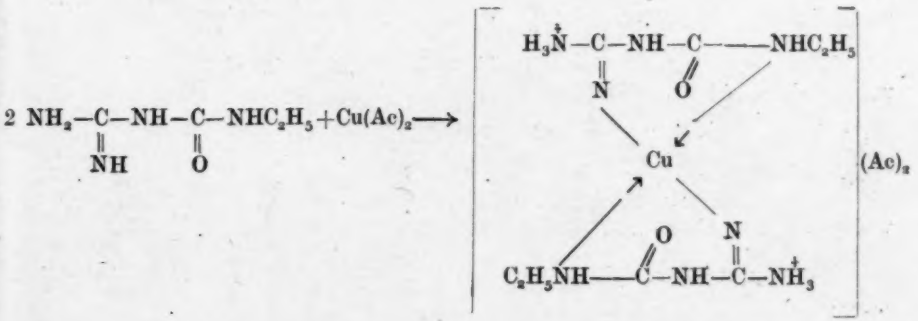
Copper(II) forms with these ligands two main types of complexes: (1) Rose-red copper-bis-guanylalkoxyethylureas formed at or above *p*H 7. These complexes are more soluble in water and ethanol than the corresponding complexes of guanylmethylurea and guanylethylurea. The molar conductance values (186-216 ohms^{-1}) indicate their bi-univalent nature. These show an absorption maximum in the range 530-540 mμ and give a paramagnetic moment value of 1.67-1.72 B.M., indicative of a square planar structure with $3d\,4s\,4p^2$ hybrid bonds. (2) Blue-coloured copper-mono-guanylakoxyethylureas formed from the bis-compounds at *p*H 3-4. These absorb at 650-660 mμ and are also paramagnetic (μ_{eff} 1.74-1.78 B.M.).

Nickel(II) gives rise to the yellow to orange-yellow bis-guanylalkoxyethylurea complexes. Of these, nickel bis-guanylethoxyethylurea and nickel-bis-guanylbutoxyethylurea salts change to the complex nickel base on heating with water. These are diamagnetic and show an absorption maximum at 450 mμ. These two properties provide strong support to the square planar structure of the complexes with $3d\,4s\,4p^2$ bonding.

Palladium (II) also produces pale cream-coloured bis-guanylalkoxyethylurea complexes. These are also diamagnetic, suggesting a square planar arrangement around palladium.

In part I of this series it has been reported that an alcohol and dicyandiamide react in the presence of copper acetate, leading to the formation of the copper complex of the corresponding guanylalkylurea. With ethanol, the following reactions occur:





A large number of monohydric alcohols, namely, methyl, ethyl, propyl^{i}, butyl^{n}, butyl^{i}, amyl^{i}, hexyl^{n}, cyclohexyl, and benzyl, were found to respond to this reaction. A comprehensive study of the copper (II), nickel (II), palladium (II), and cobalt (III) complexes of these ligands has also been recorded in this series (Dutta and Rây, this *Journal*, 1959, **36**, 499, 567, 576; Dutta, *ibid.*, 1960, **37**, 499; Dutta *et al.*, 1960, **37**, 565, 573, 789).

Ethylene glycol was expected to combine with two molecules of dicyandiamide. Only one alcoholic OH group, however, participated in the reaction, producing in presence of a copper salt the copper complex of guanylhydroxyethylurea (I). This conclusion was made on the basis of the analytical values of the copper complex.

$$NH_2-\underset{\underset{NH}{\|}}{C}-NH-\underset{\underset{O}{\|}}{C}-NH-CH_2-CH_2-OH$$

(I)

Furthermore, the copper complexes, derived from the reaction of monohydric alcohols with dicyandiamide, were stable enough to be formed by prolonged heating under reflux on a boiling water bath. This, however, was not the case with ethylene glycol. The complex copper acetate had to be obtained by heating copper acetate, dicyandiamide, and ethylene glycol at 60° and that, too, for a short period. Evidently the complexes of guanylhydroxyethylurea were less stable.

In this paper we describe the results of our studies with three substituted ethyleneglycols—one of the two alcoholic -OH groups of ethylene glycol being substituted by alkoxy groups so that these behave as monohydric alcohols. These are ethylene glycol monoalkyl ethers, *i.e.*, the alkoxyethanols, commercially known as cellosolves (methyl, ethyl and butyl cellosolves).

$$OH-CH_2-CH_2-OR$$

(II)

$$NH_2-\underset{\underset{NH}{\|}}{C}-NH-\underset{\underset{O}{\|}}{C}-NH-CH_2-CH_2-OR$$

(III)

[R=CH_3, C_2H_5 or C_4H_{10}]

The present paper deals with the isolation of these guanylalkoxyethylurea reagents and the preparation and properties of the copper(II), nickel (II), and palladium(II) complexes of these ligands.

When copper acetate, dicyandiamide, and the alkoxyethanols (II) are heated on the water bath, after two to three hours, a deep violet solution forms, which is filtered and is allowed to crystallise. The complex copper-bis-guanylalkoxyethylurea acetate is converted to the sulphate, then decomposed by H_2S and the reagents, guanylalkoxyethylureas (III), are isolated as their sulphate salts. These are very soluble in water and give rise to the usual reactions: with copper, rose red precipitate; with nickel, yellow precipitate; with palladium, pale cream-coloured precipitate in alkaline medium.

The copper (II) complexes described in this paper are of the following different types:

(1). Copper-bis-guanylalkoxyethylureas, $[Cu(Gau)_2]$, where GauH is a molecule of guanylalkoxyethylurea. These are obtained as rose-red crystalline precipitates by the addition of alkali to an aqueous solution of the complex copper-bis -guanylalkoxyethylurea acetate or chloride. The substances can be readily purified by crystallization from hot ethanol. These do not suffer any loss on reasonable heating, thus confirming the anhydro-base formula and indicating that the ligands have one acidic- NH group and another NH_2-group to function as a donor—thus behaving as bidentate units. On heating with ammonium salts these liberate ammonia with the formation of the corresponding copper-bis-guanylalkoxyethylurea salts. These are, unlike the complex of parent guanylurea, stable to hot water or ethanol.

(2). Copper-bis-guanylalkoxyethylurea salts, $[Cu(GauH^-)_2]X_2.nH_2O$, where X= CH_3COO, $\frac{1}{2}SO_4$, Cl, I, NO_3, NO_2, ClO_4, $\frac{1}{2}S_2O_6$, $\frac{1}{2}CrO_4$. These are all rose-red to red-violet in colour excepting the chromate, which is yellow. The molar conductance values (186.6, 216.8, 208.4 $ohms^{-1}$) of the complex copper chloride salts of these guanylureas in water are in fair agreement with that for bi-univalent electrolytes. The solubility of these complexes calls for comment.

In the series of the guanylalkylureas, the solubility of the complex copper chloride, acetate, or the thiocyanate in water definitely falls off with increase in the chain length of the substituent. On the other hand, solubility in ethanol increases. Thus the complex copper chloride of guanylmethylurea and of guanylethylurea are soluble in water but insoluble in alcohol; copper-guanylpropylurea chloride is soluble in water and also in ethanol, whereas those of guanylbutylurea, guanylamylurea, guanylhexylurea, and guanylcyclohexylurea are insoluble in water but readily soluble in ethanol. In fact, the complex copper-guanylmethylurea chloride and guanylethylurea chloride are only moderately soluble in water and can be easily salted out by 0.2*M*-KCl (cf. Dutta, this *Journal*, 1960, **37,** 501). The copper complexes of guanylmethoxyethylurea and of guanylethoxyethylurea are, in particular, highly soluble in water (also in ethanol)—much more so than those of guanylmethylurea or guanylethylurea. Thus crystals separate only when the solutions are highly concentrated. Even the usually insoluble salts, e.g., nitrate, bromide, iodide, perchlorate, etc., are comparatively soluble in water and even more so in ethanol. The solubility of the guanylbutoxyethylurea complexes, however, is lower than the other two. Unfortunately, we cannot comment on the solubility of the complexes of guanylpropoxyethylurea as we had no propoxyethanol at our disposal. In this context, we may mention that the copper complexes of alkoxyalkylbiguanides were found to be much more soluble than those of the alkylbiguanides (Sengupta and Rây, this *Journal*, 1959, **36,** 373,). The strength of the ligand field around copper(II) is generally reflected in the isolation of salts, such as, the iodide, thiocyanate, and the thiosulphate. In the series of the guanylalkylureas, the iodide and/or the thiocyanate salts have been described in most cases (cf. Part II, *loc. cit.*). In the present series, only the complex copper iodide of guanylmethoxyethylurea has been obtained in a pure state. With the other two ligands, addition of KI to the aqueous solution of the complex copper acetates liberates much iodine and an oily mass is left, indicating partial reduction of copper (II) to copper (I).

The chloride salts show in ethanol medium a rose-coloured hue with an absorption maximum at 530-540 m μ (ϵ 39-41). Ethanol was chosen as the solvent so that changes of hydrolysis would be the least.

The complexes have μ_{eff} values in the range of 1.67-1.72 B.M. (cf. Table III). According to Rây and Sen (this *Journal*, 1948, **25,** 475), the somewhat lower values of the mag-

netic moments indicate these complexes to be of the square planar type with $3d4s4p^2$ bonds.

(3). Copper monoguanylalkoxyethylurea chloride are blue in colour and are formed from the rose-red bis-complexes by treatment with dilute HCl (*p*H 3-4). At a *p*H 6-7 these complexes change to the rose-red bis-complexes.

$$2\left[\underset{\text{(Blue)}}{\text{Cu}\begin{matrix}\text{GauH}\\ \text{Cl}_2\end{matrix}}\right] \rightleftharpoons [\text{Cu}(\text{GauH})_2]\text{Cl}_2 + \text{CuCl}_2$$

In Part II of this series (*loc. cit.*) the mono-complexes of guanylmethylurea and of guanylethylurea only were described. These complexes exhibit an absorption maximum at 650-660 mμ and are also paramagnetic (μ_{eff} 1.74-1.78 B.M. Table III). The magnetic moments of copper-mono-guanylmethylurea chloride and copper monc-guanylethylurea chloride are also recorded for the sake of comparison. The values are in agreement with those (μ_{eff} 1.75-1.81 B,M.) reported by Rây and Das Sarma for some copper monobiguanide complexes (this *Journal*, 1951, **28,** 347).

TABLE I

Conductance measurements in aqueous solution.

I. Copper bis-guanylmethoxyethylurea chloride.

Dilution (in litres) ..	64	128	256	512	1024
Λ_v ..	72	81.5	87.3	86.4	99.8
Λ_∞ ..	84.5	91.5	94.8	91.7	104.1

Λ_∞ (mean) = 93.3
Mol. conduc. = 186.6

II. Copper bis-guanylethoxyethylurea chloride.

Dilution .. (in litres)	64	128	256	512	1024
Λ_v	77.9	91.1	100.7	110.3	117.0
Λ_∞	91.4	102.2	109.3	117.0	122.0

Λ_∞ (mean) = 108.4.
Mol. conduc. = 216.8

III. Copper bis-guanylbutoxyethylurea chloride.

Dilution .. (in litres)	64	128	256	512	1024
Λ_v	76.8	86.3	95.9	105.5	113.2
Λ_∞	90.1	96.8	104.2	112.0	118.0

Λ_∞ (mean) = 104.2
Mol. conduc. = 208.4

IV. Nickel bis-guanylmethoxyethylurea chloride.

Dilution (in litres)	64	128	256	512	1024
Λ_v	80.3	93.5	101.7	110.3	115.1
Λ_∞	94.2	104.9	110.4	117.0	120.0

Λ_∞ (mean) = 109.3
Mol. conduc. = 218.6

The nickel (II) complexes are of two types: (1) $[(Ni\ (Gau)_2]$. These yellow-coloured compounds have the composition of anhydro-bases, insoluble in water but readily soluble in ethanol from which medium purification is effected. The complex nickel bases of guanylmethoxyethylurea and of guanylethoxyethylurea liberate ammonia on warming with an aqueous solution of ammonium salts and produce the corresponding salt of the $[Ni\ (GauH_2)]^{2+}$ ion. But similar treatment decomposes the complex nickel base of guanylbutoxyethylurea. This suggests weaker basic nature as also lower stability of the complex. (2) $[(Ni\ (GauH)_2]$-$X_2.n.H_2O$, where $X = Cl$, $\frac{1}{2}SO_4$, NO_3, NO_2, $\frac{1}{2}S_2O_6$, etc. These are all orange-yellow in colour. The chloride salt is obtained by treating the complex nickel base of guanylmethoxyethylurea and guanylethoxyethylurea with dilute HCl in aqueous solution and then precipitating with acetone. From this salt, other salts have been obtained by metathesis with appropriate alkali metal salts in aqueous-alcoholic medium. The solubility of these nickel complexes, however, is much less than the corresponding copper complexes. The complex nickel bases of guanylmethoxyethylurea and guanylethoxyethylurea could be treated with dilute acids in aqueous medium to furnish salts of the type $[(Ni(GauH)_2]^{2+}$, whereas the complex nickel base of guanylbutoxyethylurea decomposed under similar treatment in aqueous medium. This base could, however, be neutralised with ethanolic dilute HCl in ethanol medium to produce the chloride salt. The chloride salt, however, decomposes to the base readily on treatment with hot water. The change occurs possibly through the formation of the hydrated base:

$$[Ni(GauH)_2]Cl_2 + 2H_2O \longrightarrow [Ni\ (GauH)_2]\ (OH)_2 + 2HCl \longrightarrow [Ni(Gau)_2] + 2H_2O$$

The aqueous solution of the complex nickel-bis-guanylethoxyethylurea chloride turns turbid on standing due to a similar change to the insoluble complex nickel base. The corresponding solution of the nickel-bis-guanylmethoxyethylurea is more stable. This points towards a decrease in the stability from guanylmethoxyethylurea to the guanylbutoxyethylurea through guanylethoxyethylurea. The corrsponding copper complexes are far too stable to undergo such a change to the complex base. This is an indication of the higher stability of the copper complexes. In this context it may be mentioned that the complex nickel base of the parent compound, guanylurea, changes readily into the simple nickel salts in neutral or a slightly acid solution so that no salt of the complex nickel-guanylurea base could be prepared (Rây and Bandapadhyay, this *Journal*, 1952, **29**, 865). A study of the dissociation constant of these guanylalkoxyethylureas and of the stability of the copper and nickel complexes are therefore expected to throw more light into such behaviour of these complexes. We propose to undertake such a study in future.

The aqueous solution of the complex nickel-bis-guanylmethoxyethylurea is stable enough to allow measurements of the conductance at various dilutions. The Λ_∞ values calculated from the Λ_v values by Walden's formula (cf. Parts II-VI, *loc. cit.*) are in very close agreement with those of a bi-univalent electrolyte (cf. Table I). Conductance values of the other two nickel complexes had to be measured in methanol. The Λ_v values are, however, somewhat lower than the limiting value (105 $ohms^{-1}$) of such electrolytes in methanol. These values, when plotted against concentration, gives a straight line, which on extrapolation to zero concentration provides values of *ca.* 95 $ohms^{-1}$.

TABLE II

Conductance measurements in methanol solution.

Dilution.	Equivalent conductance (Λ_v) Nickel-bis-guanylalkoxyethylurea chloride	
	Ethoxy.	Butoxy.
256 litres	69.6	69.6
512	77.8	77.5
1024	80.6	82.5

The complex nickel bases as well as their salts have been found to be diamagnetic (Table III). In this connection some recent works on the nickel(II) complexes may be mentioned. It has been shown from ligand-field considerations that planar, tetracoordinate complexes of Ni (II) may be either paramagnetic or diamagnetic, depending on the strength of the ligand field. Bis-acetylacetonatonickel (II) has been cited as a prominent example of a planar paramagnetic material (Liehr and Ballhausen, *J. Amer. Chem. Soc.*, 1959, **81**, 528). This substance is, however, known to form a dihydrate readily, suggesting a strong tendency for the nickel(II) to become octahedrally surrounded. Molecular weight measurements in dichloromethane, again, indicate substantial polymerization. Besides, bis-(2,2,-6,6-tetramethyl-3,5-heptanediono)-nickel (II) is red, anhydrous, and diamagnetic. Again, bis-(2,2-dimethyl-3,5-heptanediono)-nickel (II) is green, paramagnetic, but interesting is the observation that the toluene solution of the compound is green at 0° and red at 50°. The nickel complex of 3-phenyl-2,4-pentanedione behaves similarly (Fackler and Cotton, *J.Amer.Chem.Soc.*,1960,**82**,5005).

Paramagnetism in these complexes may well be attributed to intermolecular association giving octahedral $4s4p^34d^2$ bondings. The nickel complexes, described in this paper, give convincing diamagnetic values. These diamagnetic values together with strong absorption bands at 450 mμ (ε 43-46) lend strong support for their square planar structure with $3d4s4p^2$ hybrid bonds. An absorption band near 400 mμ and/or diamagnetism in tetracoordinated nickel (II) complexes has been regarded as diagnostic of a square planar arrangement (Nyholm, *Chem. Rev.*, 1953, **53**, 263). Thus, the guanylalkoxyethylureas set strong enough a ligand field around nickel (II).

Palladium (II) reacts with these ligands in alkaline medium to form cream-coloured palladium-bis-guanylalkoxyethylureas. These also correspond to the composition of anhydro-bases (cf. Part V) and can be neutralised with dilute acids to form the corresponding salts. These, too, are diamagnetic (Table III) and have a square planar structure with dsp^2 bonds.

TABLE III

Magnetic susceptibilities measurements.

Substance.	$\chi_g \times 10^6$.	$\chi_M \times 10^6$.	Dia. $\times 10^6$ (corr.)	$\chi_A \times 10^6$.	μ_{eff} (B.M.).
Copper-bis-guanylmethoxyethylurea sulphate $[Cu(C_5H_{12}N_4O_2)_2]\ SO_4.H_2O$	1.956	973.2	191	1164	1.67
Copper-bis-guanylethoxyethylurea sulphate $[Cu(C_6H_{14}N_4O_2)_2]\ SO_4 \cdot 2H_2O$	1.856	1009	228	1237	1.72
Copper-bis-guanylbutoxyethylurea sulphate $[Cu(C_8H_{18}N_4O_2)_2]\ SO_4 \cdot 2.5H_2O$	1.49	907.2	281.7	1188.7	1.68
Copper-mono-guanylmethoxyethylurea chloride $[Cu(C_5H_{12}N_4O_2)\ Cl_2]$	3.884	1143	121	1264	1.74
Copper-mono-guanylethoxyethylurea chloride $[Cu(C_6H_{14}N_4O_2)\ Cl_2]\ H_2O$	3.62	1182	145.9	1327.9	1.78
Copper-mono-guanylbutoxyethylurea chloride $[Cu(C_8H_{18}N_4O_2)Cl_2]$	3.463	1165	156.6	1321.6	1.78
Copper-mono-guanylmethylurea chloride $[Cu(C_3H_8N_4O)Cl_2]$	4.483	1123	99	1222	1.71
Copper-mono-guanylethylurea chloride $[Cu(C_4H_{10}N_4O)\ Cl_2]$	4.82	1275	110.9	1385.9	1.82
Nickel-bis-guanylmethoxyethylurea $[Ni(C_5H_{11}N_4O_2)_2]$	-0.41	-155.4	-	-	Diamagnetic
Nickel-bis-guanylethoxyethylurea $[Ni(C_6H_{13}N_4O_2)_2]$	-0.47	-191.2	-	-	,,
Nickel-bis-guanylbutoxyethylurea $[Ni(C_8H_{17}N_4O_2]_2]$	-0.35	-162.0	-	-	,,
Nickel-bis-guanylmethoxyethylurea sulphate $[Ni(C_5H_{12}N_4O_2)_2]\ SO_4, 1.5H_2O$	-0.31	-155.4	-	-	,,
Palladium-bis-guanylmethoxyethylurea $[Pd(C_5H_{11}N_4O_2)_2]$	-0.20	-85.4	-	-	,,
Palladium-bis-guanylethoxyethylurea $[Pd(C_6H_{13}N_4O_2)_2]$	-0.25	-114.0	-	-	,,
Palladium-bis-guanylbutoxyethylurea $[Pd(C_8H_{17}N_4O_2)_2]$	-0.56	-286.0	-	-	,,

EXPERIMENTAL

Copper Complexes

Copper-bis-guanylmethoxyethylurea Acetate.—Copper acetate (25 g.), dicyandiamide (25 g.), and methyl cellosolve (10 c.c.) were refluxed on the water bath for 3-4 hours. The dark rose-red solution along with some crystals was transferred to a beaker and allowed to stand overnight. Next day the crystals were filtered, dissolved in hot water or ethanol, filtered, and allowed to crystallize in vacuum. This is highly soluble in water and ethanol but insoluble in acetone.

Base.—An aqueous solution of the complex copper acetate was treated with NaOH solution when the crude base separated. This was purified by recrystallization from hot ethanol. This is insoluble in water but soluble in ethanol and acetone. This reacts alkaline to litmus and liberates ammonia on heating with ammonium salts.

Chloride.—The complex copper acetate (1 g. in 10 c.c. water) was treated with a large amount of KCl and the solution allowed to stand in the frigidaire for a day or two when rose-red crystals separated. These were filtered, dissolved in hot ethanol, filtered from the contaminated KCl, and allowed to crystallize in vacuum. This is readily soluble in water and ethanol but insoluble in acetone.

The other salts were obtained by metathesis between the complex copper acetate and the appropriate alkali metal salt in aqueous medium and whenever possible purified by recrystallization from water or ethanol. The nitrate, bromide, iodide, and the perchlorate have appreciable solubility in warm water or ethanol.

Copper-mono-guanylmethoxyethylurea Chloride.—Copper bis-guanylmethoxyethylurea chloride was dissolved in little water and the solution treated with dilute HCl till the colour changed from red violet to intense blue (*p*H 3-4). This was then dried in vacuum. The blue and rose-coloured residue was treated repeatedly with cold methanol containing a drop or two of dilute HCl, when a clear blue crystalline powder was left. The was filtered, washed with acidic (HCl) methanol, and dried in air. The washings of this preparation on standing provided another crop of light blue crystals.

Copper-bis-guanylethoxyethylurea Chloride.—The complex copper-bis-guanylethoxyethylurea base (obtained from the acetate by the action of NaOH) was neutralised with dilute HCl, filtered, and the violet-red solution allowed to crystallize in *vacuo* over H_2SO_4.

Other complexes of copper were obtained by following similar procedures as described above. In Tables IV, V and VI are recorded the analytical results of the copper (II) complexes.

TABLE IV

Complex compounds of copper with guanylmethoxyethylurea.

		Found.	Calc.
1. Copper-bis-guanylmethoxyethylurea [Cu (x)$_2$]	Cu	: 16.81%	16.64%
	N	: 30.06	29.35
2. Acetate [Cu (xH)$_2$] (CH$_3$COO)$_2$	Cu	: 12.90	12.66
3. Sulphate [Cu(xH)$_2$]SO$_4$.H$_2$O	Cu	: 12.71	1i76
	N	: 21.95	22.51
	SO_4	: 18.95	19.30
	*H$_i$O	: 3.20	3.61

TABLE IV (contd.)

		Found.	Calc
4. Chloride $[Cu(xH)_2]\ Cl_2.H_2O$	Cu :	13.25	13.44
	N :	24.16	23.70
	Cl :	15.00	15.03
5. Bromide $[Cu(xH)_2]\ Br_2.2H_2O$	Cu :	11.10	10.96
	Br :	27.30	27.59
	H_2O:	7.00	6.21
6. Iodide $[Cu(xH)_2]I_2.2.5H_2O$	Cu :	9.24	9.31%
	I :	36.95	37.20
	H_2O:	6.20	6.59
7. Nitrate $[Cu(xH)_2]\ (NO_3)_2.2.5H_2O$	Cu :	11.61	11.50
8. Perchlorate $[Cu(xH)_2]\ (ClO_4)_2.0.5H_2O$	Cu :	11.00	10.73
	N, :	19.22	18.93
9. Nitrite $[Cu(xH)_2]\ (NO_2)_2.1.5H_2O$	Cu :	12.66	12.64
10. Dithionate $[Cu(xH)_2]\ S_2O_6.1.5H_2O$	Cu :	10.95	11.13
	H_2O:	4.40	4.73
11. Copper-mono-guanylmethoxy-	Cu :	21.40	21.57
ethylurea chloride $[Cu(xH)\ Cl_2]$	N :	19.07	19.02
	Cl :	23.80	24.12

*H_2O by loss at 110°.
xH stands for a molecule of guanylmethoxyethylurea, $C_5H_{12}N_4O_2$.

TABLE V

Complex compounds of copper with guanylethoxyethylurea.

		Found.	Calc.
1. Copper-bis-guanylethoxyethylurea	Cu :	15.41%	15.51%
$[Cu(x)_2]$	N :	27.37	27.35
2. Acetate $[Cu(xH)_2]\ (CH_3COO)_2$	Cu :	11.37	11.23
	H_2O:	6.50	6.36
3. Sulphate $[Cu(xH)_2]\ SO_4.2H_2O$	Cu :	11.68	11.68
	N :	20.10	20.60
	SO_4 :	17.86	17.66
	H_2O:	6.26	6.62
4. Chloride $[Cu(xH)_2]Cl_2.3H_2O$	Cu :	11.50	11.83
	N :	20.66	20.87
	Cl :	13.21	13.23
	H_2O:	9.30	10.07
5. Nitrate $[Cu(xH)_2](NO_3)_2.3H_2O$	Cu :	10.80	10.77
	H_2O:	10.00	9.16
6. Dithionate $[Cu(xH)_2]\ S_2O_6.2.5H_2O$	Cu, :	10.27	10.30
	H_2O:	6.90	7.30
7. Copper-mono-guanylethoxyethylurea chloride	Cu :	19.56	19.45
$[Cu(xH)Cl_2]H_2O$	N :	17.30	17.15
	Cl :	21.50	21.74

xH stands for a molecule of guanylethoxyethylurea $C_6H_{14}N_4O_2$.

TABLE VI

Complex compounds of copper with guanylbutoxyethylurea.

		Found.	Calc.
1. Copper-bis-guanylbutoxyethylurea $[Cu(x)_2]$	Cu :	13.60%	13.64%
	N :	23.72	24.05
2. Acetate $[Cu(xH)_2]$ $(CH_3COO)_2.2H_2O$	Cu :	10.40	10.22
	H_2O:	6.00	5.79
3. Sulphate $[Cu(xH)_2]$ $SO_4.2.5H_2O$	Cu :	10.55	10.44
	SO_4 :	15.50	15.77
	H_2O:	7.00	7.39
4. Chloride $[Cu(xH)_2]$ $Cl_2.1.5H_2O$	Cu :	11.14	11.23
	N :	20.30	19.81
	Cl :	12.41	12.56
5. Nitrate $[Cu\ (xH)_2]$ $(NO_3)_2.3H_2O$	Cu :	9.81	9.84
	H_2O:	9.00	8.36
6. Copper-mono-guanylbutoxyethylurea chloride $[Cu(xH)Cl_2]$	Cu :	18.54	18.87
	N :	16.62	16.64
	Cl :	21.50	21.10

xH stands for a molecule of guanylbutoxyethylurea, $C_8H_{18}N_4O_2$.

Nickel Complexes

Nickel-bis-guanylmethoxyethylurea Base.—Copper-bis-guanylmethoxyethylurea sulphate was suspended in water, treated with H_2S, filtered, and the filtrate treated with air till free of H_2S. Nickel acetate was then added and the solution made strongly alkaline. The precipitated yellow complex nickel base was filtered, washed with water, and purified from hot ethanol.

Chloride.—The complex nickel base was triturated with HCl (dil.) to a faintly acid reaction when a deep orange solution formed. This solution was treated with acetone and allowed to stand overnight in the cold. The dark orange crystals were filtered, washed with acetone, and dried in air. This is readily soluble in water and ethanol.

The other salts were obtained as for the complex copper salts. Nickel complexes of guanylethoxyethylurea were also obtained by the above procedures.

Nickel-bis-guanylbutoxyethylurea Chloride.—The complex nickel base was dissolved in ethanol, neutralised with HCl, filtered, and allowed to concentrate in vacuum. Orange-yellow crystals together with some oil separated. This was then allowed to stand in the frigidaire for several hours when the oil changed to crystals. The crystals were filtered, washed with cold aqueous ethanol, and dried over $CaCl_2$. This is readily soluble in ethanol but insoluble in water. On heating with water, the orange-yellow chloride changes to the yellow-coloured base.

The complex sulphate and the nitrate were obtained by neutralising the ethanol solution of the complex base with dilute H_2SO_4 or dilute HNO_3. The analytical results of the nickel complexes are given in Tables VII-IX.

TABLE VII

Complex compounds of nickel with guanylmethoxyethylurea.

		Found.	Calc.
1. Nickel-bis-guanylmethoxyethylurea $[Ni(x)_2]$	Ni :	15.53%	15.58%
	N :	29.25	29.73
2. Sulphate $[Ni(xH)_2]SO_4.1.5H_2O$	Ni :	11.77	11.70
	N :	21.90	22.33
	SO_4 :	18.86	19.14
3. Chloride $[Ni(xH)_2]Cl_2.2H_2O$	Ni :	11.82	12.09
	N :	22.55	23.06
	Cl :	14.95	14.62
4. Iodide $[Ni(xH)_2]I_{2\cdot2}.5H_2O$	Ni :	8.97	8.90
	I :	38.73	38.49
	H_2O :	4.82	4.09
5. Nitrate $[Ni(xH)_2](NO_3)_2.4H_2O$	Ni :	10.12	10.21
	H_2O :	12.20	12.53
6. Dithionate $[Ni(xH)_2]S_2O_6.3H_2O$	Ni :	9.81	9.90
	H_2O :	9.60	9.11

TABLE VIII

Complex compounds of nickel with guanylethoxyethylurea.

		Found.	Calc.
1. Nickel-bis-guanylethoxyethylurea $[Ni(x)_2]$	Ni :	14.20%	14.50%
	N :	27.00	27.67
2. Sulphate $[Ni(xH)_2]SO_4.2H_2O$	Ni :	11.01	10.90
	N :	20.34	20.87
	SO_4 :	18.10	17.82
3. Chloride $[Ni(xH)_2]Cl_2.3H_2O$	Ni :	10.80	11.04
	Cl :	13.43	13.35
	H_2O :	9.42	10.10
4. Nitrate $[Ni(xH)_2](NO_3)_2.3.5H_2O$	Ni :	9.87	9.88
	H_2O :	11.01	10.61
5. Nitrite $[Ni(xH)_2](NO_2)_2.0.5H_2O$	Ni :	11.74	11.56
	N :	1.90	1.77
6. Dithionate $[Ni(xH)_2]S_2O_6.2H_2O$	Ni :	9.88	9.74
	H_2O :	6.20	5.97

TABLE IX

Complex compounds of nickel with guanylbutoxyethylurea.

		Found.	Calc.
1. Nickel-bis-guanylbutoxyethylurea $[Ni(x)_2]$	Ni :	12.87%	12.74%
	N :	24.33	24.30
2. Sulphate $[Ni(xH)_2]SO_4$	Ni :	10.75	10.51
	N :	20.60	20.05
	SO_4 :	17.68	17.19
3. Chloride $[Ni(xH)_2]Cl_2.H_2O$	Ni :	10.38	10.64
	N :	20.70	70.30
	Cl :	13.75	12.87
4. Nitrate $[Ni(xH)_2](NO_2)_3$	Ni :	10.34	10.00

Palladium Complexes

Sodium chloropalladite was added to the freshly prepared solution of the reagents (obtained from the complex Cu salts by H_2S, as described above under nickel) and the solution made strongly alkaline with NaOH. The precipitated complex palladium base was further purified for hot ethanol.

{Found: Pd, 25.62; N, 25.85. $[Pd(C_5H_{11}N_4O_2)_2]$ requires Pd, 25.13; N, 26.37%}.

{Found: Pd, 24.00; N, 24.70. $[Pd(C_6H_{13}N_4O_2)_2]$ requires Pd, 23.57; N, 14.74%}.

{Found: Pd, 20.83; N, 21.65. $[Pd\ (C_8H_{17}N_4O_2)_2]$ requires Pd, 20.97; N, 22.02%}.

Reagents

Guanylmethoxyethylurea Sulphate.—Complex copper-bis-guanylmethoxyethylurea sulphate (10 g.) was finely powdered, suspended in water (20 c.c.), treated with H_2S, filtered, and the filtrate treated with air till free of H_2S. The solution was then filtered, cooled in ice, and treated with acetone when an oil separated, which on scratching changed into colorless crystals.

The other two reagents also separated initially as oil, but on repeated scratching with fresh acetone, these changed into crystalline form. Because of the very high solubility of the reagents in water, no further purification was attempted.

{Found : N, 26.80; SO_4, 22.79. $(C_5H_{12}N_4O_2)_2.H_2SO_4$ requires N, 26.79; SO_4, 22.96%}.

{Found : N, 22.70; SO_4, 22.02. $(C_6H_{14}N_4O_2)_2.H_2SO_4.H_2O$ requires N, 24.14; SO_4, 20.69.%}.

{Found : N, 22.45; SO_4, 19.53. $(C_8H_{18}N_4O_2)_2.H_2SO_4$ requires N, 22.31; SO_4, 19.13%}.

Magnetic Measurements

The magnetic moments were obtained by the Gouy method using a semi-micro Mettler balance for measuring the difference in weight and a field strength of 9.26 gauss. Pascal's constants were used in calculating the corrections for the diamagnetism of the ligands (Selwood, "Magnetochemistry").

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Zinc Chloride-Phosphorus Oxychloride: A New Reagent in Organic Chemistry

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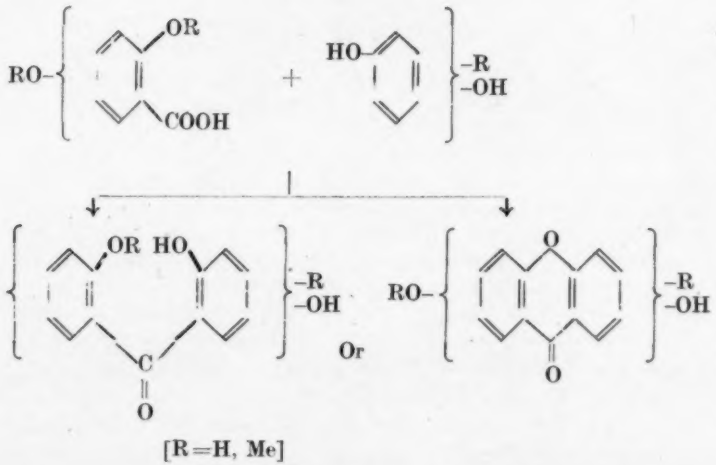
A mixture of anhydrous zinc chloride and phosphorous oxychloride in certain proportions has been found to be surprisingly effective in a number of condensations in which the individual reagents are either ineffective or only slightly effective. This new reagent has been successfully used to bring about a number of condensations under comparatively mild conditions, sometimes even at the room temperature, providing good yields of the required products.

The new reagent was first used by Shah and Mehta (this *Journal*, 1936, **13**, 368) for a successful synthesis of 2,4-dihydroxybenzophenone from benzamide or benzanilide and resorcinol. The use of this new reagent was revived recently by Grover, Shah, and Shah (*Chem. & Ind.*, 1955, 62; *J. Chem. Soc.*, 1955, 3982) who found that hydroxybenzophenones and hydroxyxanthones could be obtained in good yields by reacting *o*-hydroxybenzoic acids or their methyl ethers with polyhydric phenols or their methyl ethers in presence of the new reagent. It was also found that individually, anhydrous zinc chloride or phosphorus oxchloride was ineffective or only silghtly effective in these condensations under the same conditions.



[R=H, Me]

The efficiency of the new reagent is unique in view of the fact that other well-known condensing agents, such as, anhydrous aluminium, ferric, and, stannic chlorides, and their mixtures with phosphorus oxychloride were found to be ineffective in this reaction.

This method thus constitutes a new and convenient synthesis of hydroxybenzophenones and hydroxyxanthones. The earlier method for the synthesis of hydroxyxanthones

by heating a mixture of phenols and *o*-hydroxybenzoic acids with acetic anhydride at a high temperature (200°) afforded often poor yields and sometimes led to side reactions owing to the comparatively drastic reaction conditions (Michael, *Amer. Chem. J.*, 1883, **5**, 81; Kostannecki *et al.*, *Ber.*, 1891, **24**, 1896, 3981, et. seq; Lund *et al.*, *J. Chem. Soc.*, 1953, 2438). As compared to this, very mild reaction conditions, such as, keeping the reaction mixture at the room temperature or heating it at 60-75° for a short period, are employed in the new method which usually furnishes good yields of hydroxyxanthones.

In this new method, hydroxyxanthones are obtained directly when the acid component is a 2,6-dihydroxybenzoic acid, such as, γ-resorcylic acid or phloroglucinol carboxylic acid, or when the phenolic component is either phloroglucinol or orcinol. This instantaneous cyclisation of the intermediate 2,6-dihydroxybenzophenones in these cases may have a stereochemical significance. In other cases hydroxybenzophenones are obtained which can be further converted to the corresponding xanthones by heating with water under pressure at 180-200° (Grover, Shah and Shah, *loc. cit.*; Shah and Shah, *J. Sci. Ind. Res.*, 1956, **15B**, 630; Dalal and Shah, *Chem. & Ind.*, 1957, 140; Kane, Kulkarni, and Shah, *J. Sci. Ind. Res.*, 1959, **18B**, 28).

Several hydroxybenzophenones, viz., 2, 4,2′-trihydroxy-3′-methyl-, 2,4,2′-trihydroxy-4′-methyl-, 2,3,4,2′-tetrahydroxy-, 2,4,2′,4′-tetrahydroxy-, 2,2′-dihydroxy-4,4′-dimethoxy-, 2,3,4,2′- tetrahydroxy-3′-methyl-, 2,3,4,2′-tetrahydroxy-4-′methyl-, 2,4,2′,3′4′-pentahydroxy-and 2, 3, 4, 2′, 3′, 4′-hexahydroxy-benzophenones were prepared conveniently by this method and cyclised to the corresponding hydroxyxanthones. Similarly, a number of hydroxyxanthones, viz., 1-hydroxy-3-methyl-, 1-hydroxy-3,5- dimethyl-, 1-hydroxy-3,6′,-dimethyl-, 1,3-dihydroxy-, 3,8-dihydroxy-, 1,3-dihydroxy-5- methyl-, 1,3-dihydroxy-6-methyl-, 1,6-dihydroxy-3-methyl-, 1,8-dihydroxy-3-methyl-, 1-hydroxy-5-methoxy-3-methyl-, 1-hydroxy-7-methoxy-3-methyl-, 1,3,6-trihydroxy-, 1,3,8- trihydroxy-, 3,4,8-trihydroxy-, 1,5,6-trihydroxy-3-methyl-, 1,6,8-trihydroxy-3-methyl-, 1,3-dihydroxy-5-methoxy-, 1,3-dihydroxy-7-methoxy-, 1,3-dihydroxy-8-methoxy-, 1,3,5,6-tetrahydroxy-, 1,3,6,8-tetrahydroxy-, 1,3,8-trihydroxy-5-methoxy-, and 1,3,8-trihydroxy- 7-methoxy-xanthones were obtained by the new method from the appropriate acids and phenols.

It may be noted that 2,4,2′,4′-tetrahydroxybenzophenone, which has recently been found to be a very effective ultraviolet absorber, appears to be produced commercially under the name, Uvinul D-50 by the method of Grover, Shah, and Shah (*loc. cit.*) with the modification that 85% phosphoric acid is used in addition to make the mixture easily stirrable. The yield obtained, however, is the same, viz. 75% (Kirk and Othmer, "Encyclopedia of Chemical Technology", Second Supplement, Interscience Encyclopedia Inc., New York, 1960, p894; Stanley, U.S. P, 2,854, 485/1958).

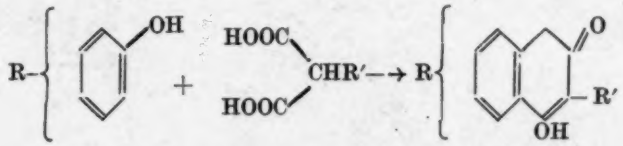
In view of the success of the new reagent in the synthesis of hydroxybenzophenones and hydroxyxanthones, investigations were carried out for its possible use in other reactions. It was found that phenols, free or protected, could be made to react with aliphatic and arylacetic acids in presence of the new reagent under mild conditions, often at the room temperature, providing good yields of the corresponding arylalkyl ketones and deoxybenzoins respectively (Bose and Shah, Indian Patents 57888/1956; 60826/1957).

This new and simple method of synthesis of aryl alkyl ketones and deoxybenzoins, in which the acids are used directly and fairly good yields are obtained, has its obvious advantages in many cases over the Friedel-Crafts, Fries, and the Hoesch reaction or methods

involving the use of more costly and hazardous condensing agents, such as, boron trifluoride or hydrofluoric acid. The following industrially important ketonic intermediates are best prepared by the method: hexylylresorcinol (75-80% yield) required for the preparation of the well-known urinary antiseptic and veterinary anthelmintic hexylresorcinol, *p*-hydroxypropiophenone (80-84%yield) required for the preparation of the synthetic oestrogen dienestrol and deoxyanisoin (80% yield), the key-intermediate for the production of the synthetic oestrogen diethylstilbestrol. In addition to these a number of other aryl alkyl ketones and deoxybenzoins were prepared by this method from the appropriate phenols and acids. These are: *p*-hydroxy- and *p*-methoxy-acetophenones, 4-hydroxy-2-methylacetophenone, *p*-methoxypropiophenone, *p*-hexylyl diphenyl ether, 4-acetyl- and 2-acetyl-1-naphthols, resacetophenone, stearoylresorcinol, γ-orcacetophenone, ω-chloroacetyl-catechol, 4-hydroxy-, 4-methoxy-, 4-phenoxy-, 4-hydroxy-2-methyl-, 4,4′-dihydroxy-, 4-hydroxy-4′-methoxy-, 2,4-dihydroxy-, 2,4-dihydroxy-4′ methoxy-deoxybenzoins, and 4-phenylacetyl and 2-phenylacetyl-1-naphthols.

A specific advantage of this method of synthesis of aryl alkyl ketones and deoxybenzoins is the almost exclusive formation of the *p*-compound in most cases.

The most important application of this new reagent so far is for the production of 4-hydroxycoumarin and its derivatives in good yields by a direct condensation of phenols with malonic acids in presence of this reagent under mild reaction conditions (Shah, Bose, and Shah, *J. Org. Chem.*, 1960, **25**,, 677; Indian Patent 62890/1958, B.P. 858110/1959). Other agents like stannic chloride, aluminium chloride, or ferric chloride, either individually or their mixtures with phosphorus oxychloride, are almost ineffective in this reaction.



[R=H, OH or alkyl
R′=H, alkyl or Ph]

The reaction between phenol and malonic acid under mild conditions, such as heating at 65-75° with the new reagent for 10-15 hrs., has furnished a high yield (60-65%) of the industrially important compound, 4-hydroxycoumarin, which is the key-intermediate for the production of a number of leading anticoagulant drugs like dicoumarol, tromexan and warfarin sodium, and also for the synthesis of modern anticoagulant rodenticides, warfarin and fumarin. This new one-stage process for the preparation of 4-hydroxycoumarin is simpler and appears to be more economic than the known methods for its manufacture, which involve two or more stages and require either costly starting materials or relatively drastic reaction conditions necessitating the use of costly equipments or complicated processing.

The following 4-hydroxycoumarins were prepared by this method: 4-hydroxycoumarin, 6-methyl-, 7-methyl-, 8-methyl-, 5,8,-dimethyl-, 5-methyl-, 8-isopropyl-, 1-thio-, 3-phenyl-, 6-phenyl-, 3-ethyl-, 3-propyl^{n}-, 3-butyl^{n}-, 3-hexyl^{n}, 3-4, octyl^{n}-, 4-hydroxycoumarins, 4-hydroxy-5,6- and 7,8-benzo-coumarins, 4, 7-dihydroxycoumarin, 4,4′-dihydroxy-6,6′-dicoumarin.

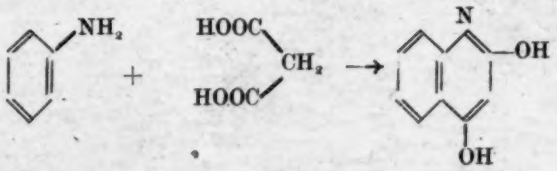
This reaction between a phenol and a malonic acid to afford 4-hydroxycoumarins

probably proceeds *via* monophenyl malonate formed as an intermediate. This was supported by the fact that monophenyl malonate gave 4-hydroxycoumarin in the presence of the new reagent.

Small amounts of diphenyl malonate were found to be formed as a byproduct in the new method for the preparation of 4-hydroxycoumarin. That diphenyl malonate was not an intermediate in the new synthesis was shown by the fact that pure dipenyl malonate alone or a mixture of phenol and malonic acid in the molar proportion of 2:1 failed to produce any appreciable quantity of 4-hydroxycoumarin in presence of the new reagent. In the latter case diphenyl malonate was obtained as the main reaction product. It was found, however, that 4-hydroxycoumarins could be obtained in good yields if diaryl malonates were heated with one mole of the corresponding malonic acid in presence of the new reagent. This reaction constituted another new synthesis of 4-hydroxycoumarins (Shah, Bose, and Shah, *Chem. & Ind.*, 1960, 623; Indian Patent 63083/1958).

The following 4-hydroxycoumarins were prepared by this method: 4-hydroxycoumarin, 6-methyl-, 7-methyl-, 8-methyl-, 5-methyl-8-isopropyl-, 1-thio-, 3-octyl[n]-4-hydroxycoumarins, and 4-hydroxy-7,8-benzo- and 4-hydroxy-5,6-(or 6,7)-benzocoumarins.

Analogous to the one-stage synthesis of 4-hydroxycoumarins from phenols and malonic acids is the new general synthesis of 2,4-dihydroxyquinoline, which has been achieved by reacting an aromatic primary amine with malonic acid in presence of the new reagent. This simple method appears to be very convenient for the synthesis of a number of 2,4-dihydroxyquinolines, which were previously prepared by long and cumbersome methods (Shah, Bose and Shah, *J. Sci. Ind. Res.*, 1960, **19B**, 176; Indian Patent 65777/1958.)



The following 2, 4 dihydroxyqinolines were prepared by this method: 2,4-dihydroxyquinoline, 6-chloro-, 7-chloro-, 5,8-dichloro-, 6-methyl-, 7-methyl-, 8-methyl-, 6-methoxy-, 8-methoxy-, and 3-octyl- 2,4-dihydroxyquinolines, 2,4-dihydroxy-7,8-benzo-, 2,4-dihydroxy-5,6 (or 6,7)-benzoquinolines, and 1,2-(2,4-dihydroxy-7, 8-pyridyl)-anthraquinone.

Aniline and malonic acid in presence of the new reagent furnished fairly good yield of 2,4-dihydroxyquinoline. It was also found that the same reaction could be brought about by phosphorus oxychloride alone, but the product was more difficult to purify. This latter procedure has been recently reported also by Zieglar and Gelfert (*Mh. Chem.*, 1959, **90**, 822).

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Reduction of Esters to Related Alcohols

J. N. Ray, Abhijit Mukherji, and Nirmalendu Datta Gupta

Aluminium amalgam in alcohol has been found to be an efficient reducing agent for converting an ester grouping to the related alcohol. The method is easy to perform in the laboratory and is superior to other methods, when small quantities are to be reduced. Coper-chromium oxide method is hardly worthwhile with small quantities.

Bouveault-Blanc reduction of esters (*Compt. rend.*, 1903, **136**, 1676; *Chem. Zentrl.* 1903, II, 418; *Bull. soc. chim.*, 1904, **31**, 666; Hansley, *Ind. Eng. Chem.*, 1947, *iii* **39**, 55) is the only method of converting esters into related alcohols, both in the laboratory and in large-scale practice. This method is not entirely satisfactory from the point of view of yield and the ease of operation on a large scale. The other method of producing alcohols in the laboratory, apart from high pressure reduction, is to convert acids into acid chlorides and then reduce them to aldehydes catalytically and thence to alcohols by standard methods.

Catalytic hydrogenation over copper-chromium oxide under high pressure is now being increasingly used in industry, but in every-day laboratory practice with small quantities it is not very feasible.

Aluminium with a standard electrode potential of -1.67 volts should serve as a good reducing agent though less powerful than metallic sodium (E_0=-2.71 volts). The usually inert aluminium becomes highly reactive due to removal of the oxide layer from the surface of the metal. It is also possible that in amalgam formation two of the valency electrons of aluminium become temporarily concerned with the two electrons of mercury, leaving one electron of aluminium in a slightly different status. Whatever may be the reason, there is a striking similarity between sodium and amalgamated aluminium. It occurred to us that esters could possibly be reduced by amalgamated aluminium to alcohols in the manner of the Bouveault-Blanc reaction. This expectation has been fully justified. We have found that ethyl benzoate is reduced to benzyl alcohol, ethyl phenylacetate to phenyl ethyl alcohol, and ethyl phenylpropionate to phenyl propyl alcohol. In every case tried, the reaction is facile and reasonably good yields are obtained. In some cases yields are diminished due to inherent difficulty of isolating the end product. The alcohol used had water in it and the reaction was not hindered in any way. We found best yields with 95% alcohol. In some cases it is better to add water to the reaction mixture as the reaction proceeds so that the strength of alcohol remains 95% (*ca*).

The most striking case was the reduction of *o*-acetoxymethyl salicylate. The product isolated was *o*-ethoxysalicyl alcohol. We are at present unable to provide a clear picture of the mechanism of the reaction. It was thought that the acetoxy group was double decomposed by aluminium ethoxide, forming aluminium acetate and *o*-ethoxymethyl salicylate in the first stage, and then this was reduced to ethoxysalicyl alcohol in the normal manner. But this view does not seem to be correct as using methanol we have not been able to isolate *o*-methoxysalicyl alcohol. The reaction remains largely incomplete and the

only recognisable product that can be isolated in very poor yield is *o*-ethoxysalicyl alcohol. Moreover, by increasing the quantity of water in the alcohol used in reduction, the yield of *o*-ethoxysalicyl alcohol was not much diminished. In the presence of a relatively large amount of water, aluminium ethoxide would have been decomposed to a large extent and would not have been available for the double decomposition reaction. Therefore we are inclined to the view that the group $-O-COCH_3$ was reduced to $-O-CH_2CH_3$. If this view is correct, then it must be regarded as a most remarkable case of reduction. The facile reduction of diethyl phthalate to phthalyl alcohol makes us think that aluminium amalgam is indeed a powerful reducing agent and its possibilities are immense. The reduction of heterocyclic esters should give valuable intermediates for synthetic work.

We are naturally extending the reaction to cover as large a field as possible.

EXPERIMENTAL

Reduction of Ethyl Benzoate to Benzyl Alcohol

Ethyl benzoate (30 g.), dissolved in hot 95% ethanol (150 c.c.) (temperature 70°), was treated with aluminium (20 g., freshly amalgamated in 4 portions). The amalgam was not dried. The mixture was thoroughly shaken. Water (30 c.c.) was added during the course of reduction to maintain the temperature at about 75°. After the whole of aluminium had reacted, the mixture was filtered and washed with hot ethanol (250 c.c.). After removal of the ethanol from the filtrate, the residue was taken in a solvent, dried, and then distilled; b.p.205°; carbanilate m.p. 78°; yield 20 g.

Phenyl ethyl alcohol was similarly prepared from ethyl phenylacetate (30 g.) and aluminium (15 g.) in hot ethanol (200 c.c.). After removal of the ethanol from the filtered reaction mixture, the residue was taken up in ether whence the product (20 g.), b.p. 220°, was obtained. α-Naphthylcarbamate, m.p. 119°, was crystallised from hot ethanol.

Phenyl Propyl Alcohol.—The reduction was carried out as described before. Ethyl phenylpropionate (17 g.) Al (6 g.), ethanol (150 c.c.) were used. After the reduction was complete, ethanol was removed by distillation. Aluminium hydroxide was then dissolved with hydrochloric acid and the whole thing extracted with chloroform. From the dried chloroform solution, the product was isolated by distillation; b. p. 235°; phenylurethane m.p. 46-47°; yield 60% of theory. When methyl cinnamate (25 g.) was reduced with aluminium (9 g.) in ethanol (250 c.c. at 75°); but no water was introduced as the reduction proceeded. (The aluminium amalgam was not dried). A crystalline substance (m. p. 172°, 6 g.) was isolated after dissolving the aluminium hydroxide in acid and hydrolysing the residue with alkali to decompose any unchanged ester. The substance was crystallised from benzene-ligroin. (Found: C, 73.4; H, 6.7%). It had no alcoholic group. It was obviously formed by a bimolecular reduction. We are investigating the nature of this substance. But in the above reduction, when water (15+5 c.c.) was introduced as the reaction proceeded, phenyl propyl alcohol (5 g.) could be isolated.

Reduction of Diethyl Phthalate: Formation of Phthalyl Alcohol

Diethyl phthalate (27 g.) in hot ethanol (350 c.c., 68-74°) was reduced with freshly amalgamated aluminium (20 g.). Water (30 c.c.) was added as the reaction proceeded to maintain the temperature to the above limits. The mixture in this experiment was very well shaken. After the amalgam was used up, ethanol was removed by distillation.

HCl was added to disssolve the precipitated aluminium hydroxide and the mixture was repeatedly extracted with chloroform. The residue from chloroform was then hydrolysed with 25% NaOH solution and extracted again with chloroform. The residue from chloroform gave the product (8-9 g.), m.p. 64-65° (cf. Perkin, *J. Chem. Soc.*, 1888, **53**, 7). The substance is sparingly soluble in benzene. On oxidation it gave phthalic acid.

Reduction of o-Acetoxymethyl Salicylate: Formation of o-Ethoxyealicyl Alcohol

o-Acetoxymethyl salicylate (25 g.) was reduced with aluminium (12 g.) in hot ethanol (150 c.c.) No extra water, except that came from the moist amalgam, was added. After removal of ethanol the mixture was treated with HCl and then repeatedly extracted with ether. The residue from ether was hydrolysed with 10% NaOH solution. Ether extract from the alkaline mixture gave an oil, b.p. 130-38°/9 mm (265°/760 mm), yield 12 g. (cf. Botsch, *Monats h*, 1880,**1**, 621). It gave *o*-ethoxybenzoic acid by permanganate oxidation.

Reduction of Diethyl Succinate: Formation of Tetramethylene Glycol

Diethyl succinate (25 g.) was reduced with aluminium (19 g.) in hot ethanol (400 c.c.). The amalgamated aluminium was added in 5 instalments. Finally water (20 c.c.) was added towards the end of the reduction and the mixture refluxed for 2 hrs. After removal of ethanol by distillation, HCl was added and the mixture was extracted with chloroform ((3×100 c.c.). The residue from chloroform was hydrolysed with NaOH (6 g. in water 20 c.c.) by heating at 100° for 2 hrs. The ice-cold solution was extracted with chloroform repeatedly whence tetramethylene glycol, b.p. 120°/10 mm (12 g.) was isolated. Dibenzoyl derivative m.p. 57-58°. The work is being continued.

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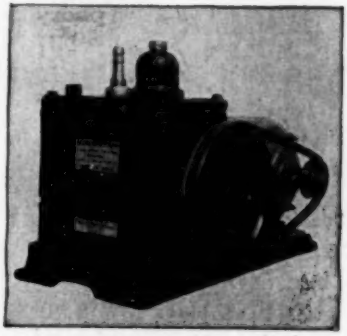

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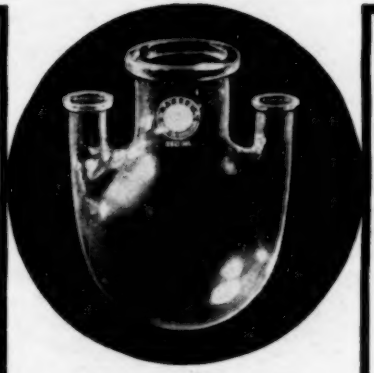

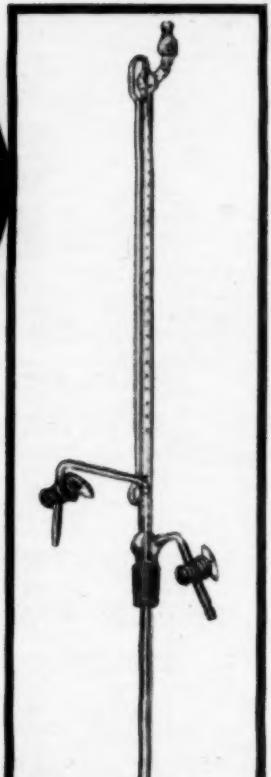

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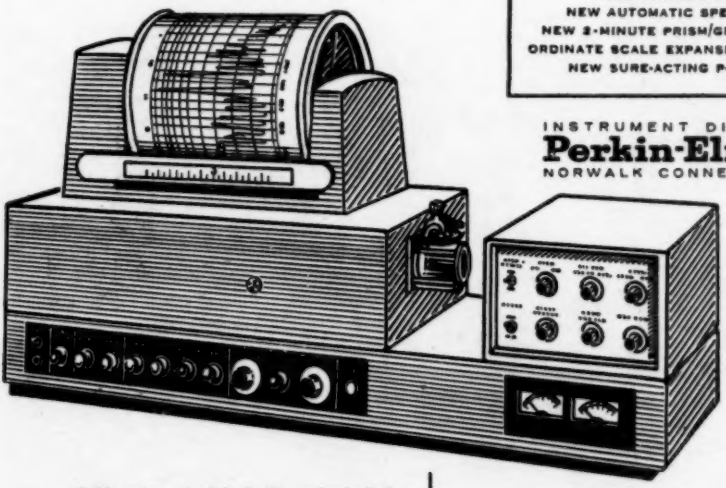

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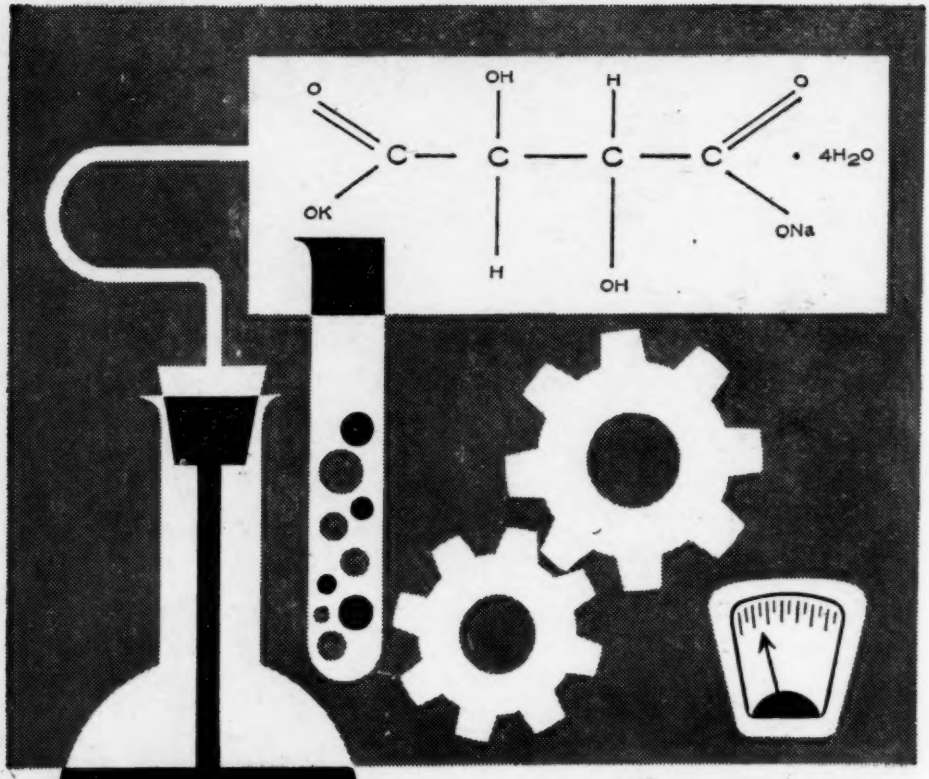

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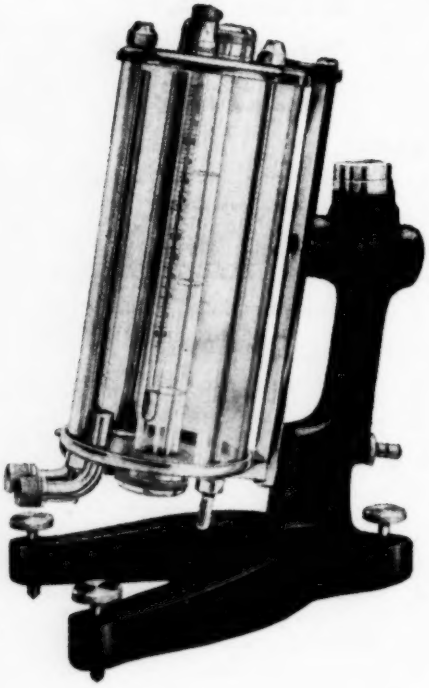

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